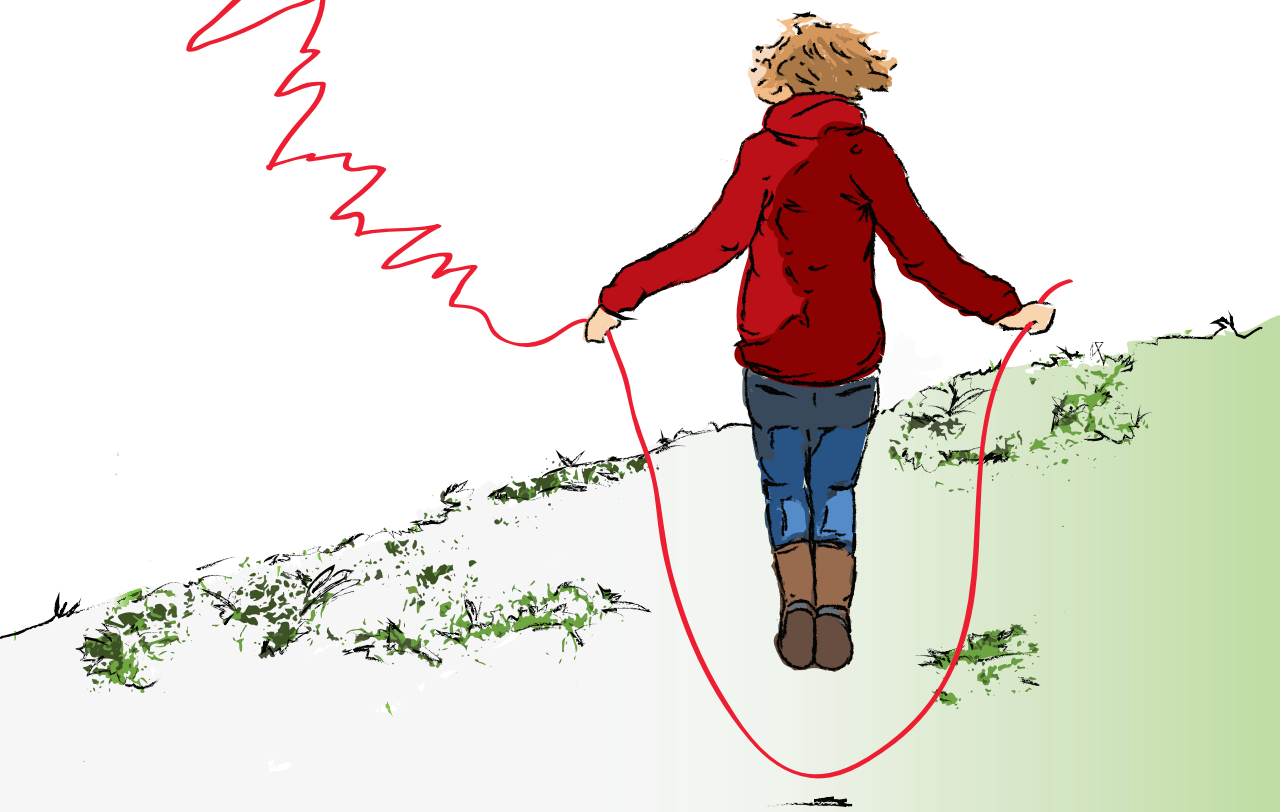
Neuronal oscillations in children with ADHD

A journey towards the development of potential new treatments for children with ADHD



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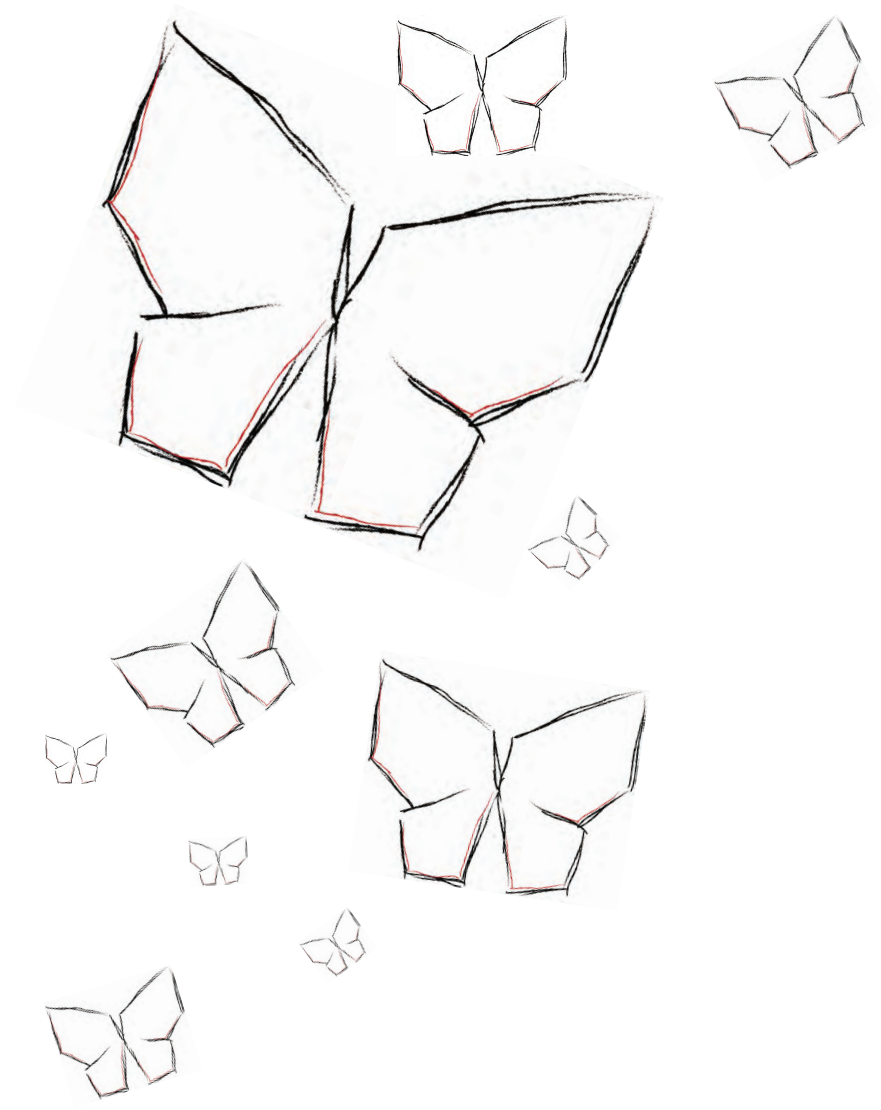

NEURONAL OSCILLATIONS IN CHILDREN WITH ADHD

A JOURNEY TOWARDS THE DEVELOPMENT OF POTENTIAL NEW TREATMENTS FOR CHILDREN WITH ADHD

Madelon Aimee Vollebregt

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“Attention is expectation, and there is no consciousness without a certain attention to life”

Bergson (1920, p. 6)

Preface & acknowledgements

This doctoral dissertation presents my journey towards the development of potential new treatments for children with Attention-Deficit/Hyperactivity Disorder (ADHD). ADHD is currently a popular research topic. At this moment, October 2015, when I search the biomedical search engine PubMed for "Attention-Deficit Hyperactivity Disorder" ("hyperkinetic reaction of childhood" and "attention deficit disorder" to find older literature), even 26,757 results are generated. What can I add to this huge pile of literature? I believe that this dissertation is a valuable addition to previous work by providing methodological sound treatment studies and a cross-sectional study investigating mechanisms underlying ADHD from a new angle. Although popular wisdom may have a negative opinion about its high estimated prevalence, we should not close our eyes, but rather face the substantial burden ADHD has on families and society.

My PhD trajectory started with a randomized placebo-controlled study in which we investigated EEG-neurofeedback as potential treatment for ADHD. When we concluded that this treatment was not superior to the placebo treatment, we created a lot of discussion and conflicting opinions in the field. Whereas a conventional dissertation may start with fundamental research leading to treatment research, our treatment study pulled me back to fundamental research. I think this dissertation shows the value of methodologically sound studies by aiming for good designs and discussing its potential drawbacks.

Before going through the studies in depth, I would like to thank all people without whom it would not have been possible to complete this dissertation. During my PhD trajectory I faced the challenge of measuring brain activity in children with ADHD; a method that required the children to sit still. In this target group sitting still is particularly difficult. Not only did I learn a lot about my research topic, I also learned a lot from interacting with children with ADHD and their parents. I am therefore grateful to have spent so many hours on neurocognitive test batteries and EEG-measurements. This part of my PhD enriched me "as a person". I therefore like to thank **all children and their parents** for participating in our studies.

This doctoral dissertation would not exist without available budget, therefore I gratefully acknowledge the partial funding by **BrainGain Smart Mix Programme** of the Netherlands Ministry of Economic Affairs and the Netherlands Ministry of Education, Culture and Science; an initiative of the Netherlands Organization for Scientific Research (NWO) to support applied research.

Furthermore, there are a number of people that I would like to thank in particular. First, I would like to thank **Jan Buitelaar**, my first promotor, for his invaluable role in the development of this doctoral dissertation. Jan, you gave me the opportunity to pursue an academic career by creating a PhD-position and by teaching me the importance of critical reflection. I could always count on feedback when needed timely. I will conserve the lessons that you taught me for the rest of my life!

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Martine van Dongen-Boosmsa, paranimph, I will not repeat the obvious; this dissertation would not exist without your input. We share quite a few publications, but more importantly; we were an excellent team! The absence of having to worry about mutual dedication is of priceless value.

Monja Froböse, paranimph, there are not many people in this world I would be able to share a house ànd an office with at the same time. With you, it did not feel like a challenge at all. Not only do I appreciate our friendship, I also greatly value your scientific view!

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Robert Oostenveld, thank you for your dedicated supervision in preparation of **Chapter 2** of this dissertation. Your technical perspective elevated the testing of our hypothesis to a higher level.

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Marieke Lansbergen, thank you for your supervision during my neuropsychology master. Your enthusiasm has triggered my interest in science.

Furthermore, I would like to thank all research colleagues and everyone from **TG** and **administrative staff** at the Donders. Together, you create such a perfect environment to do research!

Finally, I would like to thank my family and friends for putting things in perspective, with of course a special thanks to **my parents**, **Martijn** (my husband), and **Elise** (my daughter).

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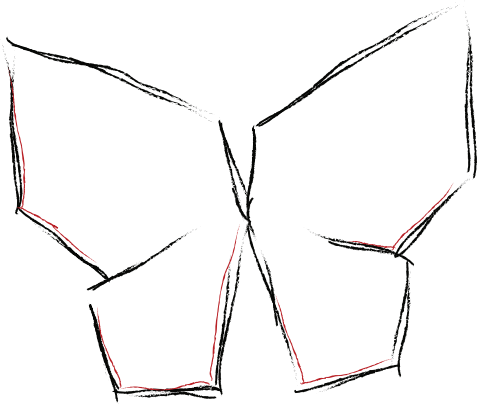


General introduction, aims and outline

This introductory chapter (**Chapter 1**) comprises a build up for the concepts of attention, ADHD, neuronal oscillations, and EEG-neurofeedback, followed by a presentation of the aims and outline of this doctoral dissertation. In the subsequent chapters (**Chapter 2-7**), six studies are presented that address the defined aims. **Chapter 2-5** focus on children with ADHD only, **Chapter 6** focuses on typically developing children only, and **Chapter 7** compares the two groups. The dissertation continues with an overview and discussion of the results in **Chapter 8** and ends with appendices (**Chapter 9**), containing a Dutch summary of the results, description of the author, and list of publications.

Attention

Imagine you are walking through the city center on a busy Saturday afternoon, looking for a store that you have not been to before and you are not sure about the exact location. In lack of time, you have to find the sign of that particular store while ignoring all other signs, all people around you, and all the tempting advertisements. Nevertheless, you will probably manage to find the store in time by selectively attending to your target and successfully ignoring irrelevant distracters.

Figure 1. Lange Hezelstraat Nijmegen, the Netherlands. To detect your target, you need to selectively attend to your target and ignore distracters.

Definition of attention

Rudimentary forms of various attentional functions are already present at birth and largely further develop during the very first year of life (Colombo, 2001). Hence, it is *in our nature* to attend to some things while ignoring others. For example, paying attention to a predator is crucial to survival, while paying attention to everything in our environment is not always beneficial.

Although we all have some idea of what attention is, defining the term entails decades of discussion already. More than a century ago, William James, psychologist and philosopher, defined attention in the following way:

> *"Every one knows what attention is. It is the taking possession by the mind, in clear and vivid form, of one out of what seem several simultaneously possible objects or trains of thought. Focalization, concentration, of consciousness are of its essence. It implies withdrawal from some things in order to deal effectively with others."*
> *(James 1890, p.403).*

A century later a new field ventured upon the topic of attention; Cognitive Neuroscience. It was Michael Posner who 'founded' the way we currently look at attention in the field of Cognitive Neuroscience. As a psychologist, Posner (1980) pointed towards different aspects of attention. He defined *orienting* as the alignment of attention with a source of input. Orienting can be overt, observable in head and eye movements, or covert, achieved by a shift of focus without head and eye movements. Posner's famous attentional cueing task was first applied in 1978 (Posner, Nissen, & Ogden, 1978), although Posner (2014) recently stated that Leonard (1953) was actually the first to develop the method. In this attentional cueing task, participants were centrally presented with a plus-sign, a left-pointing arrow, or a right-pointing arrow. The arrows validly cued the centrally fixating participant to the side of the upcoming target in 80% of the time. This allowed the investigators to study the difference in responses to validly versus invalidly cued targets, hence the influence of shifting attention.

A decade after Posner's first use of the task, Posner & Petersen (1990) attempted to overcome the earlier idea that it would be impossible to outline the functional anatomy of the human attentional system in even a preliminary form. They viewed

attention as a separate set of neural areas that interact with domain-specific systems. To this end, Posner & Petersen created a framework which divides attentional system into three subsystems; 1) *maintaining* a vigilant or alert state, 2) *orienting* to sensory events, and 3) *detecting* signals for conscious processing, and they related these subsystems to different brain areas. Two decades - and a huge pile of neuroscience literature - later, Petersen & Posner (2012) reviewed the topic again. They maintained their subsystem proposal, only now referring to it as networks rather than subsystems. They replaced the name of the first network with *alerting* and – a more significant change – the third network with *executive*, since this would capture the content better. Between 1990 and 2012, these networks had been related to different brain areas. In their review (2012), the alerting network was described to activate the primarily right lateralized fronto-parietal cortex and thalamus. The orienting network was described to activate a dorsal top-down attention network consisting of the frontal eye fields and intraparietal sulcus/superior parietal lobe. and a ventral bottom-up network consisting of the temporal-parietal junction and the ventral frontal cortex. Especially the temporal-parietal junction activity seemed to be right lateralized. The executive network was described to activate the cingulo-opercular control system and the frontoparietal system. Petersen & Posner concluded that 20 years after their first attempt to study attention from a neuroscientific perspective, current research gratifyingly allows the investigation of attention from genes to cells, networks, and behavior, and to examine age-related changes.

Occasionally, a slightly different division has been employed than the division made by Peterson & Posner, replacing orienting attention with selective attention (e.g. Parasuraman, 2000 in Tsal, Shalev, & Mevorach, 2005). Although selective attention and orienting attention are commonly used interchangeably in the literature, they are not the same; while orienting attention requires detection of a target only, selective attention requires identification of the target (Tsal et al., 2005).

Although other – comparable – divisions within attention have been made in the literature as well, this general introduction does not aim to be exhaustive in providing these divisions.

The study-design used in **Chapter 6** and **Chapter 7** was based on Posner's attentional cueing task.

Development of attention

As stated above (see *Definition of attention* in this chapter), rudimentary forms of various attentional functions are already present at birth and largely further develop during the very first year of life (Colombo, 2001). As pointed out by Posner and Rothbart (1998), it is obvious from parental observations that holding and rocking calms their infant earlier than three months, while distracting by bringing their attention to other stimuli helps calming them later. *Figure 2* shows how a three-month-old infant (my daughter, Elise) is already attentively following movements of a fish in an aquarium.

Figure 2. Three-month-old infant attentively looking at aquarium.

Developmental research of the attentional networks has shown that different networks mature at different stages (Posner et al., 2014). Luria (1973) already roughly differentiated an involuntary biological attentional system that develops early and a voluntary social attentional system that develops later. While during infancy and early childhood the orienting network exerts much of the control over brain networks (Posner et al., 2012; Rothbart et al., 2011), by 4 years the executive network start to dominate (Posner et al., 2014). The orienting network seems to reach full maturity before 6 years (Rueda et al., 2004). The executive networking shows a dramatic development around 5 years of age (Berger et al., 2007; De Luca & Leventer, 2008). The development of the executive network probably enables internally controlled goals to influence actions (Posner et al., 2014).

Typically, an asymmetric pattern between hemispheres has been observed in developing attention (Yaakoby-Rotem & Geva, 2014). Executive functioning around the age of 5 showed an advantage for the right prefrontal cortex (Rolfe, Hausmann, & Waldie, 2006). Asymmetry in attention and lateralized brain activation has been

explained in different ways. Heilman et al. (1987) suggested that the right hemisphere controls spatial attention bilaterally by orienting responses to stimuli in either visual hemifield, while the left hemisphere controls the right visual hemifield only. Kinsbourne (1987) on the other hand, suggested that both hemispheres orient spatial attention to the contralateral visual hemifield, but the left hemisphere has a stronger bias than the right hemisphere. Fully developed executive functions are thought to be necessary to overcome an inherent spatial bias towards the right visual hemifield typically observed in children (e.g., Andersson & Hugdahl, 1987; Hugdahl & Andersson, 1986; Hugdahl et al., 2009; Jurado & Rosselli, 2007; Mondor & Bryden, 1991; Posner & Raichle, 1994; Takio et al., 2009, 2011, 2013), being replaced by a bias to the left visual hemified typically observed in adults (Bowers & Heilman, 1980; Manly et al., 2005). **Chapter 6** will elaborate on the typical development of attention and its asymmetric patterns.

Attention-Deficit/Hyperactivity Disorder (ADHD)

Although attentional problems are associated with several disorders, the most typical disorder associated with such problems, is Attention-Deficit/Hyperactivity Disorder (ADHD). Although people with ADHD show difficulties in more domains than just the attentional domain, attentional deficits are a substantial part of the diagnostic core-symptoms of ADHD as defined by the *Diagnostic and Statistical Manual of Mental Disorders (5th ed. [DSM-5]*, American Psychiatric Association, 2013). To date, ADHD affects the startling amount of approximately 5–7% of the school age population, with a male to female ratio of around 3:1 in community-based samples of children and adolescents (Willcutt, 2012). Genuine etiological differences may underlie gender differences (Arnett et al., 2015), possibly explained by different genetic and cognitive liabilities in boys and girls. Even though functional impairment (Faraone, Biederman, & Mick, 2006) or subthreshold impairing symptoms (Biederman, Mick, & Faraone, 2000) often persist into adulthood, this dissertation will focus on children of 7 to 15 years old only.

Children displaying symptoms of ADHD have been described since over three centuries with the first description of ADHD symptoms dating back to at least 1775 (Barkley & Peters, 2012). However, due to different opinions and increased knowledge, the terminology of the clustered symptoms has changed over time. Currently, the fifth edition of the DSM is used as diagnostic manual (American

Psychiatric Association, 2013). The studies described in this dissertation still made use of the preceding fourth edition (*fourth ed. [DSM-IV]*; American Psychiatric Association, 2000). The diagnostic procedure is a (semi-structured) interview performed by a clinician with the parents and school, record questionnaires and observations of the child during the procedure. The diagnosis of ADHD is regarded as being reliable and valid when evaluated with standard criteria for psychiatric disorders (Faraone et al., 2015). In the fifth edition, the disorder is described as a persistent pattern of inattention and/or hyperactivity/impulsivity that started before the age of 12, that has been present for at least 6 months, is inappropriate for the developmental level of the child, is present in multiple settings (e.g., school and home), and results in lower performance in social, educational, or work settings. Furthermore, to fulfill the criteria of an ADHD diagnosis, the pattern of behavior should not happen only during the course of a psychotic disorder or be better explained by another mental disorder. A diagnosis based on the DSM-IV is largely overlapping with the DSM-V. A few differences can be found between editions with respect to diagnosing children with ADHD; the DSM-IV states that the ADHD symptoms must have started before the age of 7 rather than 12 and excludes people with autism spectrum disorder. Furthermore, even though children can display symptoms of different categories according to both editions of the manual, in the DSM-V these categories are called presentations, while they are called subtypes in the DSM-IV. The three different presentations (i.e. subtypes), are the inattentive presentation, hyperactive/impulsive presentation, and combined presentation. For children, the specific presentation is based on the presence of six or more symptoms of hyperactive-impulsive behaviors (HI) or inattentive behaviors (I), or of both dimensions (C).

Initially, brain infections (Stewart, 1970; Cantwell, 1981), trauma (Blau, 1936; Werner & Strauss, 1941), epilepsy (Holdsworth & Whitmore, 1974), and complications during pregnancy and delivery (Shirley, 1939) were related to impaired attention, regulation of activity, and impulsivity. Since most children with ADHD do not have a history of such damage, brain injuries are unlikely to account for the majority of children with this disorder (Rutter, 1977). However, symptoms of ADHD do resemble those following lesions or injuries to the frontal lobes (Mattes, 1980; Benton, 1991). Several genetic and environmental risk factors are thought to have joint small individual effects on the susceptibility of ADHD (Faraone et al., 2015). This complex causation is consistent with the heterogeneous expression of the disorder. Heterogeneity is evident by its neurocognitive impairment in multiple domains, its extensive psychiatric co-

morbidity, and the wide range of structural and functional brain anomalies (Faraone et al., 2015). Often, neurocognitive impairments are described within attention (described later in this paragraph), executive functions, reward-related processes, and timing. Probably the most reliable discriminator between ADHD and typically developing controls – although not specific to ADHD – is a difference in response time variability measured across different tasks and methods (for meta-anlytic review, see Kofler et al., 2013). There is however no consensus between different models that aim to explain the cause of this difference in response time variability yet (Kofler et al., 2013). Impairments in executive functioning are found in domains of response inhibition, vigilance, working memory, and planning (Martinussen et al., 2005; Willcutt et al., 2005). Studies on reward-related processes in ADHD indicate a preference for small immediate rewards over larger delayed rewards (for review see Sonuga-Barke et al., 2008). Finally, with respect to timing both temporal processing deficits and delay aversion have been observed in ADHD (Sonuga-Barke et al., 2010; de Zeeuw et al., 2012). More specifically, temporal processing deficits are found in three major domains, i.e., motor timing, perceptual timing, and temporal foresight (for review see Noreika, Falter & Rubia, 2013).
What role neurocognitive deficits play within the causal model of ADHD is not clear yet. A recent longitudinal study showed that better performance on a high executive functioning demanding task (set-shifting) at around 10 years old predicted a better clinical outcome four years later. Changes in executive functioning between 10 and 14 years old were however not associated with changes in symptoms (Coghill et al., 2014). Based on these findings, the authors of this study suggested that neurocognitive problems in ADHD might occur at the same level as core-behavioral symptoms within the causal model, potentially making independent contribution to overall impairment.

Diagnostic core-symptoms in the attentional domain encompass problems in all attention networks defined by Peterson & Posner (2012); *maintaining* attention (e.g. "has difficulty sustaining attention in tasks or play activities"), *orienting* attention (e.g. "is easily distracted"), and *executive functioning* (e.g. "has difficulty organizing tasks and activity"). Although verifying the presence of these different aspects of attention is part of the diagnostic process by performing a (semi-structured) interview and record questionnaires, very few scientific studies directly examined performance on specific aspects of attention in ADHD. A study that did investigate different aspects of attention, found that children with ADHD on group-level suffered from deficits in all studied attentional domains (Tsal et al., 2005), but only deficits in

maintaining attention characterized almost all studied children with ADHD. Deficits in orienting of attention, executive attention, and selective attention (requiring identification of the target in addition to orienting to it (see *Definition of attention* earlier in this chapter), characterized only half of the group (Tsal et al., 2005). The fact that *any six of nine core-symptoms* lead to a diagnosis means that ADHD is very heterogeneous at the phenotypic level; in turn, this might explain the large variety in attentional and cognitive difficulties within the ADHD group. As predicted based on the diagnostic system, studies with large sample sizes do find a difference between ADHD and controls on selective attention (Johnson et al., 2008) while smaller group studies do not (Huang-Pollock & Nigg, 2003). Differences in study results can be explained by the use of different instruments to examine the different aspects of attention. More importantly, neurocognitive factors are more vulnerable to context or temporary changes during measurement while symptoms are assessed using the whole developmental history (Kendler & Neale, 2010). Fair et al. (2012) showed that neuropsychological trait variation in typically developing children could inform the heterogeneity within children with ADHD.

Following from the idea that detection of a target slows detection of another target (Duncan, 1980 in Peterson & Posner, 2012), the executive network (entailing target detection according to Petersen & Posner) seems to be responsible for preventing interference of distractors. Interference of distractors under low perceptual load has been shown to be different in children with ADHD from typically developing children (Chan et al., 2009). Moreover, children with ADHD were distracted more in the right visual field at a mean age of 11.7 years old while their 11-year-old peers without ADHD were distracted more in the left visual field. The magnitude of interference for right-sided targets was correlated with ADHD severity (Chan et al., 2009). Keep in mind the above discussed typical development in which an age-related reduction of a rightward bias is observed (rightward bias no longer present at 10-11 years old) (see *Development of attention* in this chapter, Takio et al., 2013).

To understand the underlying mechanism of the behavioral symptoms and neurocognitive deviations of ADHD, measurements of neuronal activity in these children may provide insight. Approaches in this direction are to measure event related potentials (ERPs) or neuronal oscillations through electro encephalography (EEG), which are assumed to directly reflect neuronal activity. **Chapter 2** and **Chapter 7** of this dissertation focus on the latter.

Neuronal oscillations

EEG is a neuroimaging technique that was introduced by Hans Berger early in the 19th century (1929). It aims to measure electrical currents of cells that fire synchronously from the scalp by measuring electric field differences. Because measures are from the scalp, the originating source can be located far from the measurement point/electrode, thereby causing a relatively poor source localization and spatial resolution but good temporal resolution. An EEG signal consists of a sum of neuronal oscillations at different frequencies, phases, and amplitudes. These neuronal oscillations can be studied separately after transforming the signal using a *Fourier Transformation*. Oscillations represent rhythmic or repetitive neural activity in the central nervous system.

Different characteristics of neuronal oscillations can be studied, such as its power, peak frequency, coherence (e.g. Klimesch, Sauseng, & Hanslmayr, 2007), modulation, topography, and classification (e.g. Horschig et al., 2014). In this dissertation, the focus was on power (squared amplitude [the maximum extent of an oscillation]) and peak frequency (frequency [number of cycles per second] within a frequency band with the highest power) of the studied neuronal oscillations. *Figure 3g* gives a visual illustration of these definitions. Note that power can be studied in an absolute or relative way. There is no superior one, but it is important to be aware of its difference. Relative power is less sensitive to individual variation by accounting for the variation in thickness and resistance of the skull than absolute power, which is sometimes – but not always – preferred.

Electrophysiological frequency bands

Oscillations have traditionally been grouped into different frequency bands and these bands have been associated with different brain functions. For an overview of commonly studied different frequency bands, see *Figure 3*. Different frequency bands have been associated with different particular functions. It has been suggested that oscillations in the lower frequency ranges are associated with long-range connectivity between cortical regions, which are crucial for integration of information (Nunez, 1995), while oscillations in the higher frequency ranges (~gamma) seem to reflect the local firing pattern of neurons (Schurmann et al., 1999).

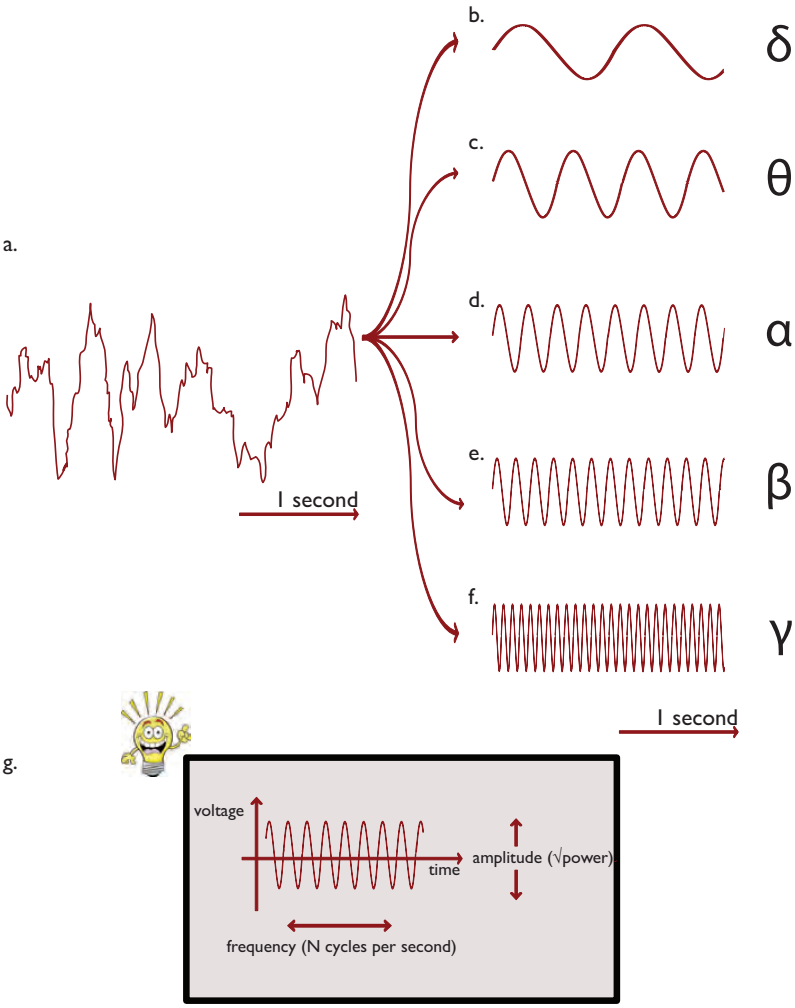


Figure 3. (*a*). The raw EEG-signal. Activity from different frequency bands are extracted from the raw EEG-signal by using a Fourier transformation. (*b-f*). Different frequency bands, indicated by corresponding Greek letters. (*b*). Delta oscillations (< 4 Hz). (*c*). Theta oscillations (4-8 Hz). (*d*). Alpha oscillations (8-12 Hz). (e). Beta oscillations (12-30 Hz. Often split into beta-1/sensorimotor rhythm [SMR], 12-16 Hz, and beta-2, 17-30 Hz.) (*f*). Gamma oscillations (>30 Hz). (*g*). Visual illustration of the different studied characteristics of neuronal oscillations.

Delta oscillations have been associated with evolutionary old basic processes, which are under normal circumstances overshadowed by higher frequency oscillations representing more advanced processes in awake adults. These slow oscillations are thought to influence motivational drives, emotional appraisal, salience detection, subliminal perception, and emotional learning (for review, see Knyazev, 2012). Delta oscillations were not specifically studied in this dissertation.

Theta oscillations have been related to active memory maintenance by showing a frontal increase with the number of items retained in working memory (Jensen & Tesche, 2002). Furthermore, theta oscillations were consistently observed during REM sleep and transitions to wake in the hippocampus and during transitions from sleep to wake and in quiet wakefulness in the basal temporal lobe and frontal cortex (Cantero et al., 2003). In infants and pre-school children, oscillations in the theta-band have been strongly related to behavioral states with substantial attentional and emotional load (Orekhova et al., 2006). Theta oscillations were directly or indirectly studied in **Chapter 2-5**.

Oscillations in the alpha range were discovered along with the advent of EEG. They were initially known for its appearance when closing the eyes (Berger, 1929) and they are still seen as a measure for resting-state arousal (Barry et al., 2007). However, evidence is building up for a more active role of alpha oscillations, gating streams of information through the brain by means of its modulation as proposed by the alpha inhibition hypothesis (Klimesch et al., 2007). The functional role of alpha oscillations are further discussed in *Modulation of alpha oscillations* in this chapter. Alpha oscillations were directly or indirectly studied in all chapters of this dissertation.

The functional role of beta-band oscillations is less clear-cut (Engel & Fries, 2010). Traditionally, oscillations in the beta-band have been associated with the motor system (Pfurtscheller & Lopes da Silva, 1999) and they are still thought to be part of the large-scale sensorimotor network (van Ede & Maris, 2013). Aiming at a unifying hypothesis regarding the functional role of beta-band activity, Engel & Fries (2010) proposed that oscillations in this frequency-range play a central role in the maintenance of cognitive and sensorimotor states both within *and* outside of the motor system. A computational model proposed that alpha-band oscillations may be produced by a thalamo-cortical feedforward drive, while beta-band oscillations need an additional feedback from higher order cortical areas (Jones et al., 2009). Beta oscillations were, like theta oscillations, directly or indirectly studied in **Chapter 2-5**.

Finally, oscillations in the gamma frequency-range have been related to attentional selection via neuronal synchronization, to working memory via maintenance of synchronous firing, and to long-term memory because of its phase-specific synaptic input that is thought to facilitate synaptic plasticity and thus encoding of long-term memory (for review, see Jensen, Kaiser, & Lachaux, 2007). Frontal gamma is thought

to act as *the central executive* in Baddeley & Hitch's (1974) working memory model (Lutzenberger et al., 2002; Haegens et al., 2010). In addition, collaboration between gamma and alpha power seem to create pulses of inhibition; higher alpha power was associated with a stronger suppression of gamma activity at a given alpha phase, thereby pulsing active inhibition (Bonnefond & Jensen, 2015). Gamma oscillations were not specifically studied in this dissertation.

In sum, this dissertation mainly focused on the theta-, alpha-, and beta-band, with a specific focus on the alpha-band in **Chapter 6-7**.

Resting state neuronal oscillations in children

A large study of developmental changes in EEG performed in 1973 showed that delta- and theta activity decreased with age, dominating other frequency bands until the age of 4 years, while alpha- and beta activity increased with age during childhood (Matoušek & Petersén, 1973). The authors concluded that slower band activity might be substituted by faster band activity with development (Matoušek & Petersén, 1973). This conclusion was supported in later findings by Matthis et al. (1980) and Gasser et al. (1988a).

With respect to topographic developmental differences in EEG, different studies reported changes as well. Matoušek & Petersén (1973) found that developmental changes in the EEG were observed in posterior areas before changes in more frontal areas. Also, the theta activity decrease compared to alpha activity increase was double as fast in occipital areas than in central areas (Benninger, Matthis, & Scheffner, 1984). Changes in the delta, theta, and alpha frequency bands were first observed in occipital areas, then parietal, central and lastly frontal areas (Gasser et al., 1988b). For the beta band, these changes started in central areas, then more posterior, and again lastly frontal (Gasser et al., 1988b). The midline showed developmental changes before the two hemispheres did (Clarke et al., 2001a).

Focusing on alpha oscillations, early resting-state studies by Lindsley (1936, 1938) and Smith (1937, 1938a, 1938b, 1939) showed that 3 – 4 month old infants already have an occipital alpha-like rhythm at 3 – 4 Hz. In a subsequent longitudinal study, Lindsey (1939) pointed out that the frequency of the alpha waves rapidly increased during the first year of life, slower during the years after to become relatively

constant from 12 years old onwards. The amplitude increased during the first year or two whereafter it strongly decreased during the third year and less strong the years after to become relatively constant from 15 – 16 years onwards (Lindsey, 1939). Overall, literature suggested that the alpha frequency increases from early childhood to adulthood and then decreases with aging (for review, see Klimesch, 1999). The 6–9 Hz band has shown to be a useful alpha-band from the end of the first year of life into early childhood (Marshall, Bar-Haim, & Fox, 2002), while the alpha-band studied in healthy adults is usually around 10 Hz (for review, see Klimesch et al., 2012). Hence, the individual frequency at which alpha is peaking seems to be lower in children than in adults.

These changes in activity and distribution of neuronal oscillations in different frequency bands show that neuronal oscillations are not static, but develop with age. Also due to its developmental changes, deviant neuronal oscillations can be expected in a neurodevelopmental disorder such as ADHD and may provide inside in the underlying mechanism of the behavioral symptoms and neurocognitive deviations of ADHD.

Resting state neuronal oscillations in ADHD

Early studies in children with behavioral problems corresponding with those of the current concept of ADHD indicated 'EEG slowing' (Jasper, Solomon & Bradley, 1938), in a frequency range we would now refer to as the theta-band. Elevated absolute theta power is nowadays the most consistent finding in children with ADHD, as became apparent in a recent meta-analysis of studies on oscillatory activity at the vertex during an eyes-open resting-state condition in children with ADHD (Arns, Conners, & Kraemer, 2013). Resting-state theta power has been positively correlated with inattention on symptomatic (Loo et al., 2004; Ogrim, Kropotov, & Hestad, 2012) and neurocognitive levels (Hermens et al., 2005; Swartwood et al., 1998; Swartwood et al., 2003; Loo & Smalley, 2008) and negatively correlated with hyperactive/impulsive symptoms (Ogrim et al., 2012). Decreased resting-state beta power has also been found in ADHD but far less consistently; 13 – 20% of children with ADHD showed elevated beta- power and spindles (Arns, Conners, & Kraemer, 2013). The relationship between beta power and ADHD symptoms has also yielded inconsistent results. Findings suggest that absolute beta power is correlated positively with inattention and the overall symptom score of ADHD (Ogrim et al., 2012),

while other findings suggest that beta power is correlated positively with impulsivity (Swartwood et al., 1998; Swartwood et al., 2003) and negatively with inattention (Swartwood et al., 1998). Only Ogrim et al. (2012) were explicit on having studied absolute power.

Often, the power ratio between two frequency bands (theta- and beta-band) is reported and found to be elevated at the vertex in children with ADHD compared with controls (Arns et al., 2013). Despite robust appearance with a large mean effect size of around 0.7, caution in interpretation is warranted for several reasons. First, across the years within the last decade, there has been a decrease in effect size when comparing ADHD and controls due to an increase of the theta/beta power ratio in controls (Arns et al., 2012). In line with this shift, a more recently published large study on the theta/beta power ratio, did not find a difference between ADHD and controls (Loo et al., 2013). Second, the theta/beta power ratio cannot be regarded as a reliable diagnostic tool in ADHD since discrimination accuracy between children with and without ADHD was 58% only (Ogrim et al., 2012). Third, although fixed frequency bands showed a difference in theta/beta power ratio between boys with ADHD and healthy controls, this difference was absent when using the individual alpha peak frequency to determine individualized frequency bands (Lansbergen et al., 2011a). These results suggest the existence of a group with an actual excess of theta power without any individual alpha peak frequency mediation and another group with a lower individual alpha peak frequency, which consequently "leaks" into the theta band, causing the theta-band power estimate to falsely inflate when using a fixed frequency band (Arns et al., 2012). Following the alpha inhibition hypothesis, a low individual alpha peak frequency has been hypothesized to slow the process of allowing and stopping of information transfer (Grandy et al., 2013). In the literature, the individual alpha peak frequency has been considered low if <9 Hz for children aged 9 to 17 years and <8.5 Hz for those aged 6 to 9 years (Arns et al., 2008). Such a low individual alpha peak frequency has been shown to be important because of its relation with nonresponse to stimulant medications in children with ADHD (Arns et al., 2012). Deviations in resting-state power in the alpha band have yielded inconsistent results. Large differences in the choice of data analyses and individual differences may partly account for these differences. Some studies reported absolute power differences (elevated in ADHD: Bresnahan & Barry, 2002; Koehler et al., 2009; Lazzaro et al., 1999; El-Sayed, Larsson, Persson & Rydelius, 2002, diminished in ADHD: Woltering et al., 2012), while other studies reported relative power differences

(diminished in ADHD: El-Sayed et al., 2002; Woltering et al., 2012; Clarke et al., 2001a; Barry et al., 2010, elevated in ADHD: Chabot & Serfontein, 1996; Lazzaro et al., 1999) and again other studies reported no differences (absolute power: Clarke et al., 2001a; Barry et al., 2010; Bresnahan, Anderson, & Barry, 1999; Bresnahan et al., 2006, relative power: Bresnahan et al., 1999; Bresnahan et al., 2006). Also in some studies it was not reported whether absolute or relative power was investigated (Clarke et al., 2001d; Loo et al., 2009).

Direct investigation of resting state neuronal oscillations in ADHD is described in **Chapter 2**. This chapter further describes a subgroup of children with ADHD with such a low individual alpha peak frequency that it overlaps with the conventional theta frequency band of 4-8 Hz. In **Chapter 3-5**, deviant resting state neuronal oscillations in ADHD form the basis for treatment. The majority of to dates studies investigated resting state neuronal oscillations. However, study neuronal oscillations during task performance may provide new insights. **Chapter 6-7** focus on neuronal oscillations during task performance, which will be introduced later in this chapter (see *Modulation of alpha oscillations* later in this chapter).

Training neuronal oscillations

Although more fundamental research is undeniably necessary to understand the physiological basis of ADHD (see **Chapter 2**, **6**, and **7**), there is need for acute treatment as well. It is evident that ADHD affects children's personal development substantially and is associated with impairments in social and emotional development, and poor academic and vocational outcomes (Wehmeier, Schacht, & Barkley, 2010). Consequently, the substantial burden on families and society in general is notable (Biederman, 2005; Biederman et al., 2012).

According to the guidelines from the *National Institute for Health and Care Excellences* (NICE, 2008), first-line treatment for school-aged children and adolescents with ADHD displaying moderate impairment should be – mostly group-based – education programs for parents/caregivers of school-aged children and adolescents. Then behavioral interventions, in particular parent management training should be offered. For older children this may also include group-based or individual behavioral approaches. According to the NICE guidelines, drug treatment should be reserved

for children and adolescents with severe symptoms and impairment, or who refuse non-pharmacological interventions or do not respond to psychological treatment. For severe cases, medication is regarded to be the most effective treatment; placebo-controlled studies show large effect sizes on the core ADHD symptoms for amphetamine, methylphenidate (Faraone & Buitelaar, 2010) and atomoxetine (Michelson et al., 2002; Banaschewski et al., 2008). Despite these large effect sizes, appliance to individual cases should happen with care, because only 56% of the patients in the medication group met the definition of success at the end of treatment (Swanson et al., 2001). Also, insufficient knowledge about long-term safety (Berger et al., 2008) and efficacy (van de Loo-Neus, Rommelse, & Buitelaar, 2011), continuous need for treatment (Jensen, Kaiser, & Lachaux, 2007; Murray et al., 2008), and the possible wish of the child or adolescent and/or the parents or caregivers to not follow drug treatment call for nonpharmacological alternatives. Sonuga-Barke et al. (2013) studied the efficacy of non-pharmacological treatments. More specifically, they performed a systematic review and meta-analyses on studies investigating dietary (restricted elimination diets, artificial food color exclusions, and free fatty acid supplementation) and psychological (cognitive training, neurofeedback, and behavioral interventions) ADHD treatments. From these meta-analyses, it was concluded that dietary interventions had small beneficial effects on ADHD symptoms. Behavioral/psychological ADHD treatments however, were largely influenced by the blinding procedure; results were much more positive for most proximal raters than for blinded raters. Part of these meta-analyses were the studies on electroencephalographic (EEG)-neurofeedback, described in **Chapter 3-5** of this dissertation.

EEG-neurofeedback is a treatment that makes use of measurements of neuronal oscillations through EEG. As current treatment for ADHD it usually targets the deviations of the resting-state neuronal oscillations found in children with ADHD as described above (*Neuronal oscillations in ADHD*, in this chapter). EEG-neurofeedback aims to gain control over processes underlying the neuronal oscillations that are measured, enhancing self-regulation by the use of operant learning strategies; when changes in neuronal oscillations are observed in the desired direction, simultaneous and contingent visual and/or acoustic feedback represents positive reinforcement (Gevensleben et al., 2012). The International Society for Neurofeedback and Research defined EEG-neurofeedback as: "Neurofeedback, also known as EEG-biofeedback, is a process in which sensors are placed on the scalp and devices are used to monitor and provide moment-to-moment information that is fed back to the individual about

his or her physiological brain activity for purposes of improving brain functioning" (Hammond et al., 2011). For a schematic overview of an EEG-neurofeedback set-up, see *Figure 4*.

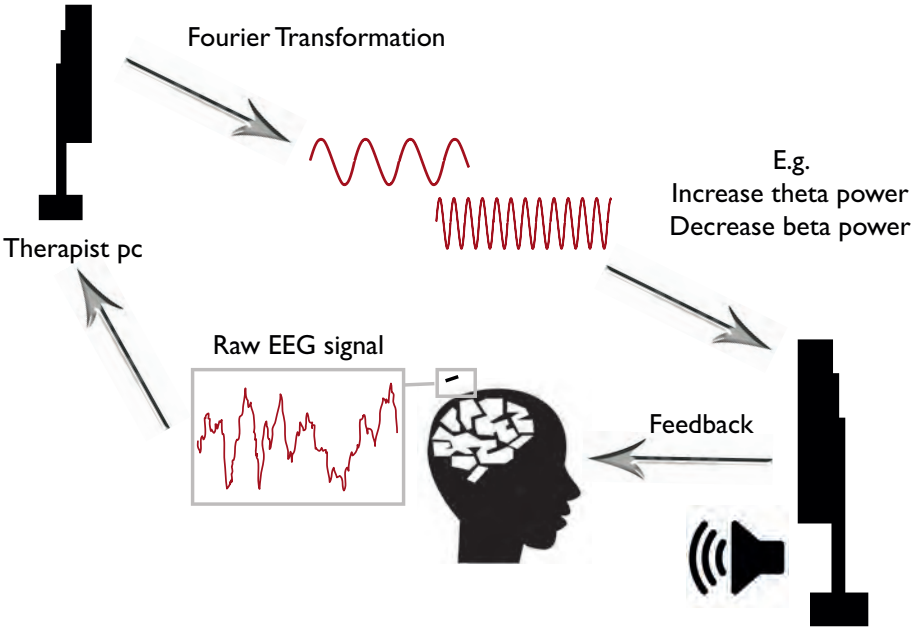


Figure 4. Schematic overview EEG-neurofeedback set-up.

The history of EEG-neurofeedback

The first publication from EEG-neurofeedback in humans dates back to 1968 (Kamiya, 1968). Participants had to report whether they were currently in "alpha-state" – associated with relaxation – or not. While participants started their reporting at chance level, during the course of the training some participants increased their ability to recognize the alpha-state and correctly answered most trials. In addition, Kamiya found that some participants were even able to enter the alpha-state on command (Kamiya, 1968). Sterman et al. discovered the positive effect of EEG-neurofeedback on patients with epilepsy not much later (Sterman, Macdonald, & Stone, 1974) by further investigating the accidentally discovered effect of EEG-neurofeedback on epileptic cats, in humans (Wyricka & Sterman, 1968). Sterman

trained cats to increase their beta-1/sensorimotor rhythm (12-16 Hz) over the sensorimotor cortex by providing milk each time they did. These trained cats had built resistance against a toxic substance known to provoke seizures. Lubar & Shouse (1976) were the first to report the effects of sensorimotor rhythm activity increase and theta activity decrease training in an 11-year old boy with hyperkinetic disorder, a disorder much alike ADHD (*second ed. [DSM-II]*; American Psychiatric Association, 1968) used to describe overactivity, restlessness, distractibility, and short attention span before ADHD in its current form (American Psychiatric Association, 2013) was diagnosed. After that, research on this topic has gained a lot of interest in a relatively short period of time, especially in the last half-decade. When a PubMed search is performed at present (October, 2015) combining the following MeSH terms; ("Attention Deficit Disorder with Hyperactivity" [MeSH terms) AND ("Biofeedback, Psychology" [MeSH terms] OR "Neurofeedback" [MeSH terms]) this yields 8165 results (*Figure 5*).

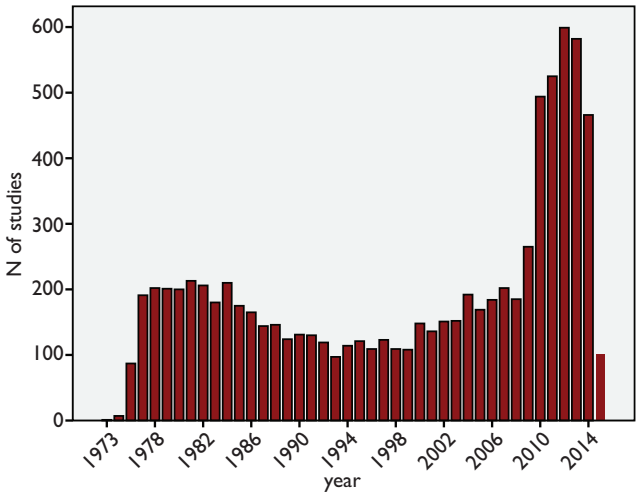


Figure 5. The number (N) of studies published per year when a PubMed search is performed (October, 2015) combining the following MeSH terms; ('Attention Deficit Disorder with Hyperactivity' [MeSH terms) AND ('Biofeedback, Psychology' [MeSH terms] OR 'Neurofeedback' [MeSH terms]).

The current state of affairs of EEG-neurofeedback

Nowadays, roughly two different forms of EEG-neurofeedback can be distinguished; frequency neurofeedback and slow cortical potential (SCP) neurofeedback. Frequency neurofeedback protocols target frequency bands known to deviate in ADHD during resting-state most often. An example of a frequency neurofeedback protocol is rewarding an increase of beta activity and a decrease of theta activity (Monastra et al., 2005; Gevensleben et al., 2012). SCP neurofeedback protocols target the lowest frequencies, reflecting cortical excitation impairment in ADHD (Sergeant, 2005; Banaschewski & Brandeis, 2007). An example of an SCP neurofeedback protocol is when changes in polarity (positive and negative shifts) over the sensorimotor cortex are rewarded (Arns et al., 2009). While frequency neurofeedback has been hypothesized to influence the tonic aspects of cortical arousal, SCP neurofeedback has been hypothesized to influence the phasic excitability (Gevensleben et al., 2009). Throughout this dissertation, the use of the term "EEG-neurofeedback" does not specify the form (frequency neurofeedback or SCP neurofeedback), but most often refers to frequency neurofeedback.

Robust evidence based on methodologically sound studies is still lacking. To date, a number of randomized controlled trials, reviews, and meta-analyses relating to EEG-neurofeedback in children with ADHD have been published. The majority of studies that conclude that EEG-neurofeedback is probably effective did not include a placebo group and/or blinded measures. Studies that did include a placebo group or a blinded design have not found superior effects of EEG-neurofeedback compared to placebo-neurofeedback (Perreau-Linck et al., 2010; Arnold et al., 2013; **Chapter 2**). Incorporating these results, a systematic review and meta-analyses of randomized controlled trials (RCTs) of non-pharmacological interventions in children with ADHD including EEG-neurofeedback studies reported non-significant results for the blind rating of symptoms (ES 0.29, $p = 0.07$; CI = -0.02, 0.61) (also described in the introduction of the current section *Training neuronal oscillations* in this chapter, and Sonuga-Barke et al., 2013).

This dissertation describes a randomized placebo-controlled study in children with ADHD in which frequency neurofeedback is being investigated. **Chapter 3** and **Chapter 4** describe the symptomatic and neurocognitive outcome of this treatment respectively. In **Chapter 5** it is extensively discussed how results of these and other studies are informative and how present methodological limitations of the current studies may be overcome.

Modulation of alpha oscillations

Albeit a substantial part, this doctoral dissertation does not only describe and discuss results of a randomized placebo-controlled study on an *existing* treatment; it aimed to take a step in the direction of the development of potential *new* treatments for children with ADHD. This step was taken towards understanding the physiological basis of ADHD by studying neuronal oscillations during task performance. In addition to studying neuronal oscillations during resting state, studying neuronal oscillations during task performance may provide new insights into understanding neuronal activity. In recent years, strong mechanistic ideas have been developed such as on the functional role of alpha oscillations. Now its time to use this insight to attempt to understand the physiological basis of ADHD.

With this aim, studying modulation of alpha oscillations during task performance may provide more information on the functional role of oscillations in this frequency band. The functional role of alpha activity in healthy adults has particularly been studied using visuospatial covert attention cueing paradigms based on variations of Posner's paradigm (see also, *Attention* earlier in this chapter). In most electroencephalography (EEG) and magnetoencephalography (MEG) investigations of covert spatial attention, a cue directs attention to the left or right visual hemifield, which allows for investigating the alpha power in the hemispheres processing the attended and unattended visual hemifields. Results repeatedly showed that posterior alpha power increased ipsilateral and decreases contralateral to the attended visual hemifield, respectively inhibiting or facilitating the information flow (Worden et al., 2000; Sauseng et al., 2005; Kelly et al., 2006; Thut et al., 2006; Händel, Haarmeier, & Jensen, 2011; Bengson, Mangun, & Mazaheri, 2012; ter Huurne et al., 2013). More importantly, high alpha power over task-irrelevant regions has been linked to the processing of the unattended information and proved to be of crucial importance for optimal attentional performance (Romei, Gross, & Thut, 2010; Händel et al, 2011).

Whether children display lateralized posterior alpha modulation with spatial attention similar to adults and whether changes in alpha power relate to behavioral performance was unclear. **Chapter 6** of this dissertation describes the –to my knowledge– first study that studied the modulation of oscillatory brain activity as recorded by EEG in relation to behavioral performance of 7 to 10 year old typically developing children performing a visuospatial covert attention task.

Alpha modulation in ADHD

A failure to modulate alpha activity during covert attention performance might be a core problem in ADHD, given the aforementioned tight links of alpha modulation with attention allocation in healthy adults as well as the observed increased distractor interference (hence reduced distractor inhibition) in children with ADHD (especially under low perceptual load in the right visual hemifield) (Chan et al., 2009). Furthermore, functional MRI studies often reported hypoactivation in the frontoparietal network in ADHD (Cortese et al., 2012). Alpha oscillations are thought to be under top-down control; they can be disrupted by applying transcranial magnetic stimulation to the contralateral frontal eye fields (FEF) (Capotosto et al., 2009; Marshall et al., 2015b). The FEF in turn, is thought to be part of the dorsal frontoparietal network for top-down control of visual attention (Corbetta & Shulman, 2002).

A study investigating alpha modulation during a cross-modal attention task in children with ADHD showed that significant alpha modulation was absent in these children (Mazaheri et al., 2010). During working memory performance, alpha activity was relatively diminished during encoding, while frontal theta activity was relatively elevated during maintenance in ADHD compared to typically developing children (Lenartowicz et al., 2014). Increased theta activity during maintainance was interpreted as a compensatory mechanism for decreased alpha activity during encoring. To my knowledge, only adults - rather than children - with ADHD were studied during covert attentional performance. These adults with ADHD demonstrated a problem in sustaining hemispheric alpha lateralization when cued to the left, resulting in an attentional bias in response times to the right visual hemifield compared to healthy adults (ter Huurne et al., 2013). **Chapter 7** of this dissertation describes the first study that compared modulation of oscillatory brain activity as recorded by EEG of 7 to 10 year old children with ADHD performing a visuospatial covert attention task with typically developing children.

Aims and outline of the dissertation

The aims of this doctoral dissertation were to answer the following research questions;

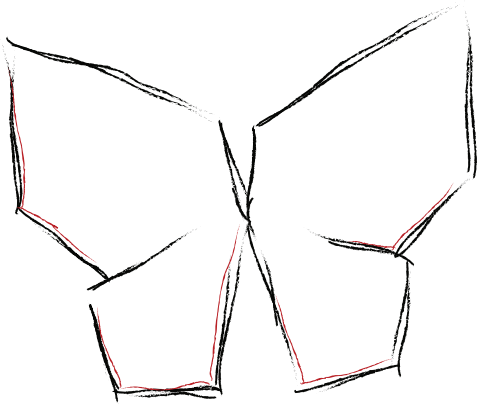
a. Is there a relationship between the theta/beta power ratio and theta power, and behavioral functioning using a broad range of behavioral measures within ADHD? Are these relationships influenced by the individual alpha peak frequency?
b. Does current daily practice EEG-neurofeedback have a positive effect on symptomatic and neurocognitive functioning in children with ADHD?
c. How do lateralized alpha modulations observed in children relate to previous observations in adults?
d. How do lateralized alpha modulations observed in children with ADHD relate to those observed in typically developing children and previous observations in adults with and without ADHD?

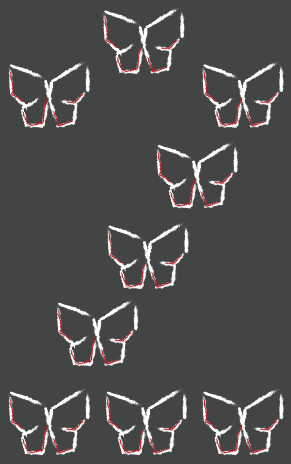
To this end, data from two different samples were analyzed.

A stratified, semi-randomized double-blind placebo-controlled treatment design was set up to answer the first two research questions (*a* & *b*). This *first sample* consisted of 41 children (age between 8 – 15 years) with a primary diagnosis of ADHD (all subtypes), based on the *DSM-IV-TR*, without any other psychiatric disorder (except for ODD and anxiety disorders) or any other serious medical condition. The use of a stable dosage of stimulants and/or atomoxetine was allowed, provided the presence of room for improvement on behavioral level. The children in this sample were semi-randomly assigned to frequency neurofeedback or placebo-feedback for 30 sessions, twice a week. Assignment was based on stratification on age, electrophysiological state of arousal, and medication use. At baseline, resting-state oscillations were measured. Before treatment and at study end, behavioral measurements were performed and a wide selection of neurocognitive tasks was administered. Baseline resting-state oscillations were explored and analyzed in relation to the performance on the neurocognitive tasks and the core-behavioral symptoms of ADHD (**Chapter 2**). Efficacy of frequency neurofeedback was measured by analyzing the difference between groups on core behavioral symptoms and global

clinical functioning (**Chapter 3**) and neurocognitive functioning (**Chapter 4**) at study end compared to baseline measurements. Furthermore, electrophysiological changes during treatment were explored by analyzing the neuronal oscillations during the sessions (**Chapter 4**).

To answer the last two research questions (*c* & *d*), a cross-sectional design was set up which allowed to compare ADHD and typical development. This *second sample* consisted of 44 children (age between 7 – 10 years). Twenty-two typically developing children and 22 children with ADHD. Typically developing children were included if 1) they had never had a psychiatric, neurological, or cardiovascular disease or serious motor or perceptual handicap, 2) they did not score in the clinical range on the ADHD DSM-IV rating scale (American Psychiatric Association, 2000) and any subscale of the Child Behavior Checklist (CBCL; Verhulst, van der Ende, & Koot, 1996), both completed by parents, and 3) their estimated IQ was above 80. Children with ADHD were included if they 1) had received a clinical diagnosis of ADHD according to DSM-IV, 2) scored in the clinical range on the ADHD DSM-IV rating scale, completed by parents, and 3) had an estimated IQ was above 80. They were allowed to take ADHD-related medication, but had to stop the medication no later than 12 hours prior to the experiment. The presence of clinical behavior on CBCL subscales other than the inattention subscale was discussed with the responsible clinicians to exclude the possibility of a co-morbid diagnosis and verify that ADHD was the primary diagnosis in all cases.
Analyses described in **Chapter 6** used 21 of the typically developing children from the second sample. **Chapter 7** describes boys from the second sample, creating a sample of 9 typically developing boys and 17 boys with ADHD.





How the alpha peak frequency helps to unravel the neurophysiological underpinnings of behavioral functioning in children with Attention-Deficit/ Hyperactivity Disorder

ADHD has been associated with an elevated resting-state theta/beta power ratio and elevated theta power. However, the potential confounding effect of a low individual alpha peak frequency (IAPF) on the theta power estimate has often been disregarded, when studying the relationship between ADHD and the theta/beta power ratio or theta power alone. The current study assessed whether the theta/beta power ratio and relative theta power correlated with behavioral functioning in children with ADHD such as expected from previous work. Subsequently, the influence of IAPF and the amount of supposed overlap between the individually determined alpha-band and the fixed theta-band were studied.

For 38 children (age between 8 – 15 years) EEG data and investigator-scored ADHD Rating Scales IV were available. Additional neurocognitive data were available for 32 children.

As expected, the theta/beta power ratio and theta were positively related to the ADHD core-symptoms. This relationship strengthened when controlling for IAPF, although correlations did not significantly differ from each other. Eight out of 38 (21%) children showed a supposed overlap between their individually determined alpha-band and the theta-band. Neurocognitive performance did not show any relationship with the theta/beta power ratio or theta power.

The results of this study confirmed that the theta/beta power ratio and theta power indeed correlated with behavioral symptoms in children with ADHD and underscore the relevance of taking the IAPF into account.

Based on
Vollebregt, M. A., Van Dongen-Boomsma, M., Slaats-Willemse, D., Buitelaar, J. K.*, Oostenveld, R.*.
***joint last authorship**

Clinical EEG and Neuroscience. 2015, 46(4), 285-291. doi: 10.1177/1550059414537257

Introduction

Children with ADHD display impairments in sustained attention and set-shifting (Weissman et al., 2012), response inhibition, vigilance, working memory, and planning (Martinussen et al., 2005; Willcutt et al., 2005), reward processing (Luman, Oosterlaan & Sergeant, 2005; Luman, Tripp & Scheres, 2010), and temporal processing (Noreika, Falter & Rubia, 2013). The persistence of these neurocognitive impairments is clinically relevant for ADHD by their strong association with impairment in global functioning (Biederman et al., 2012).

The past decades, research has been conducted to understand the neurophysiological underpinnings of behavioral (i.e., symptomatic and neurocognitive) functioning in children with ADHD using quantitative electroencephalography (qEEG). A recent meta-analysis of studies on oscillatory activity at the vertex during an eyes-open resting-state condition in children with ADHD, showed that elevated absolute power in the theta-band is reported most consistently in ADHD (Arns, Conners, & Kraemer, 2013). Resting-state theta power has been positively correlated with inattention on symptomatic (Loo et al., 2004; Ogrim, Kropotov, & Hestad, 2012) and neurocognitive level (Swartwood et al., 1998; Swartwood et al., 2003; Hermens et al., 2005; Loo & Smalley, 2008) and negatively with hyperactive/impulsive symptoms (Ogrim et al., 2012). In addition, a diminished resting-state beta power has been found, although 13 – 20% of patients with ADHD showed excess beta power or beta spindles (Arns, 2012). Other inconsistent findings suggest that beta power correlated positively with inattention and the overall symptoms-score of ADHD (Ogrim et al., 2012), but correlated positively with impulsivity (Swartwood et al., 1998; Swartwood et al., 2003) and negatively with inattention (Swartwood et al., 1998).

Elevation of the ratio between power in the theta- and beta-band has been regarded as a robust finding at the vertex in children with ADHD compared to controls (Arns et al., 2013). The eyes-closed resting-state theta/beta power ratio showed a weak correlation with inattention symptoms (Loo et al., 2013). Despite its robustness, caution in interpretation is warranted for several reasons (Arns et al., 2013). Firstly, the accuracy of discrimination between ADHD and controls based on this ratio is too low to serve as a diagnostic tool (Monastra et al., 1999; Ogrim et al., 2012). Secondly, although fixed frequency-bands showed a difference in theta/beta power ratio between boys with ADHD and healthy controls, this difference was absent using

individual alpha peak frequency (IAPF) to determine individualized frequency-bands (Lansbergen et al., 2011a). These results suggested the existence of a group with an actual excess of theta power without any IAPF mediation, and another group with a lower IAPF which consequently 'leaks' into the theta-band, causing the theta-band power estimate to falsely inflate when using a fixed frequency-band (Arns, 2012).

IAPF rises until the teenage years in healthy development (Chiang et al., 2011). Developmental change seems an important observation since ADHD is regarded as a neurodevelopmental disorder. Power in the alpha-band has been related to functional inhibition of neuronal activity and processing (Klimesch, Sauseng, & Hanslmayr, 2007). A failure to suppress incoming distracting information, hence to modulate alpha power, is per definition a present core-feature of ADHD. Alpha power modulation during task performance indeed has been shown aberrant in children and adults with ADHD (Mazaheri et al., 2010; ter Huurne et al., 2013). Following the inhibition hypothesis, a low IAPF has been hypothesized to slow the process of allowance and stopping of information transfer (Grandy et al., 2013). In the literature, IAPF has been considered low if < 9 Hertz (Hz) for 9 – 17 year old children and < 8.5 Hz for 6 – 9 year old children (Arns et al., 2008). Importantly, a low IAPF has been shown to be important by its relation with non-response to stimulant medication in ADHD (Arns, 2012). Furthermore, the IAPF is thought to be trait-like and considerably heritable (Posthuma et al., 2001; van Beijsterveldt & van Baal, 2002; Smit et al., 2010; Grandy et al., 2013) suggesting that despite changes during development, genetic factors play a lasting role.

Most research regarding these conventional electrophysiological measures focused on a dichotomous difference between ADHD and controls rather than gradual changes. The few studies that focused on gradual changes within ADHD have rather inconsistent methods and results and were not always described in sufficient detail (e.g., concerning the use of absolute or relative power and the use of correction for multiple statistical comparisons). Differences between study-designs (e.g., regarding age-range, neurocognitive tasks, and medication use) further complicate comparisons.

The aim of this study was twofold. Rather than making a dichotomous distinction between ADHD and controls, the theta/beta power ratio and theta power were first correlated with behavioral functioning using a broad range of behavioral measures. Although Ogrim and colleagues (2012) found a negative correlation between

absolute theta power and hyperactive/impulsive symptoms (rated by teacher), we expected a positive relationship, driven by the elevated theta power found in children with ADHD with an inherent clinical symptom-level of both inattention and hyperactivity/impulsivity. Likewise, a lower performance on neurocognitive tests, with a higher theta/beta power ratio and relative theta power was expected. Second, these relationships were studied while controlling for IAPF, comparing zero-correlations with IAPF controlled correlations. Also, the amount of children showing an IAPF for which overlap between individually determined alpha-band and fixed theta-band can be expected was determined. Taken together, the current study was designed to unravel the confounded interpretation of conventional electrophysiological measurements due to low IAPFs.

Methods

Participants

Data acquired from a clinical trial on EEG-neurofeedback in children with ADHD were examined (http://www.clinicaltrials.gov; NCT00723684). The study was approved by the Dutch Central Medical Ethics Committee (www.ccmo.nl) and conducted in accordance with the declaration of Helsinki. All parents and all children ≥12 years gave their written informed consent before participation; children <12 year gave oral assent. Findings related to treatment efficacy and methodological procedures have been described in detail elsewhere (**Chapter 3** and **4**). Here, we will provide the information relevant for the present study only.

Children (8 – 15 years old) with a diagnosis of ADHD classified according to the *Diagnostic and Statistical Manual of Mental Disorders (4th ed., text rev. [DSM-IV-TR]*, American Psychiatric Association, 2000) without any comorbid psychiatric diagnosis (except for oppositional defiant disorder) or any serious other medical condition. Use of ADHD-medication was allowed albeit with clinically significant remaining ADHD symptoms, i.e., at least six inattentive or hyperactive/impulsive symptoms above the clinical threshold.

Behavior

ADHD symptom rating

Total severity of inattentive and hyperactive/impulsive symptoms of ADHD, according to the *DSM-IV-TR* based ADHD Rating Scale IV (Zhang et al., 2005), was scored by the investigator in an interview with the parents, using a 4-point Likert scale (0 = never occurs, 1 = occurs sometimes, 2 = occurs often, 3 = occurs very often). The sum per subscale and the sum of all symptoms were used for further analyses.

Neurocognitive performance

Participating children underwent a neurocognitive assessment of approximately 90 minutes (min). Complete task descriptions can be found elsewhere (**Chapter 4**). Sustained attention was measured with the Sustained Attention Dots task (SA-DOTS), visuospatial memory with Visuospatial Sequencing (VSS), verbal working memory with Digit Span from the Wechsler Intelligence Scale for Children-III, verbal working and long term memory with The Rey Auditory-Verbal Learning Test (RAVLT), instrumental/operant learning with the Instrumental Learning task, precision of time perception with the Time Production task, and precision of time reproduction with the Time Reproduction task.

Electrophysiology

Instruction

EEG was acquired during 10-min eyes-open and 10-min eyes-closed resting-state conditions. Children were instructed to sit quietly and fix their eyes on one spot during the measurement. In between they had a small break.

Data processing

Data were processed and analyzed using MATLAB 2012a (The MathWorks, Inc., Natrick, MA) and the FieldTrip EEG analysis toolbox (Oostenveld et al., 2011). Data segments showing artifacts such as vertical and horizontal EOG exceeding 100 microvolt, muscle potentials, amplifier or electrode noise, were identified using a semiautomatic routine and excluded from further analysis. When less than two minutes data remained within a dataset, the EEG signal quality was regarded inadequate and the subject was excluded from further analysis.

EEG system

EEG was recorded from 21 scalp electrodes placed according to the 10-20 system using the TruScan EEG system (DEYMED Diagnostic, Payette, ID). Electrode impedance was kept below 10 kOhm. Electrode Fpz was used as ground and the common reference was placed just anterior of electrode Fz. For all, but 8 children EEG data were recorded with a bandwidth of 0.1 – 102 Hz and the sampling rate was 256 Hz. For 8 children EEG data were recorded with a bandwidth of 0.1 – 64 Hz and a sampling rate of 128 Hz. Eye movements were not separately recorded but were detectable in the frontal EEG channels.

Electrophysiological procedure

First, spectrally resolved power was calculated using a Fast Fourier Transform. To make an informed choice of analysis parameters and to limit the number of EEG variables, i.e., minimize multiple statistical comparisons for the subsequent analysis, we used literature and a pilot analysis on independent data (see *Independent pilot study* in appendix of this chapter for details). These resulted in a selection of relative theta power at the vertex for further analyses. The theta/beta power ratio was included based on literature findings. The condition, electrode position, and bandwidth of theta and beta were chosen to be consistent with (most) studies from the recent meta-analysis on the theta/beta power ratio (Arns et al., 2013); power was estimated at electrode Cz at the vertex for theta (4 – 8 Hz) and beta (13 – 21 Hz) frequency-bands in the eyes-open condition, using a time windows of 1 second (s) and a Hanning taper. The theta/beta power ratio was calculated by dividing the average power over frequency bins within the theta-band by the average power over frequency bins within the beta-band. Theta was derived by dividing the average power over frequencies within the theta-band by the overall power of all frequencies measured at that electrode.

To investigate the possibility of alpha-band power leaking into the theta-band estimate, the IAPF was determined. *Figure 1* depicts how the IAPF may confound the estimate of theta power using illustrative data from two children. Obviously, higher alpha power influences the theta-band power estimate more. However, to limit the number of statistical comparisons, only IAPF was a-priori selected for this study. To yield an accurate estimate of the IAPFs, we constructed a power spectrum with higher resolution than used in the standard analysis. Time windows of 3 s were Hanning windowed and Fourier transformed, resulting in 1/3 Hz frequency

resolution. The IAPF was determined by the maximum power attenuation between the eyes-open and eyes-closed condition within 6 – 15 Hz at the occipital electrodes (average O1 and O2). All outcomes were checked by visual inspection without prior knowledge on any of the other outcome variables. In case of multiple peaks, the peak closest to 10 Hz was chosen. Next, recognition of the determined peak was verified at the vertex.

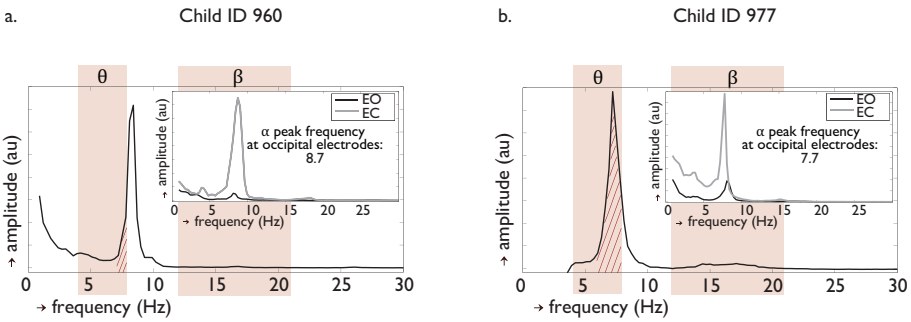


Figure 1. This figure shows two data-set examples how activity from the alpha-band may lead to false interpretations of the theta-band power estimate. For illustrative purposes, the 1/f component has been removed from the power spectra in this figure. The fixed frequency bands are depicted with the shaded areas and corresponding Greek letters (θ=theta; β=beta). The striped area under the alpha-curve indicates the area in which alpha power may falsely be estimated as theta power. The smaller graphs depict the eyes open and eyes closed conditions in the occipital channesl with which the individual alpha peak frequency was determined. (*a*). A case in which a – somewhat low – alpha peak frequency results in 'leaking into' the theta power estimation. Since the amplitude, hence the power of alpha is at least three times higher than of theta, this small overlap with the theta-band will inflate the theta power estimate. (*b*). A case in which the frequency of the alpha peak is clearly low, resulting in even more 'leakage' into the theta power estimation. Note that with a same peak frequency, a higher alpha amplitude (i.e., power) would have a bigger influence on the theta power estimation.

Abbreviations: au: arbitrary units; Hz: Hertz; EO: Eyes Open; EC: Eyes Closed; α: alpha

Statistics

Statistical analyses were performed with IBM SPSS Statistics, version 20.0 (Armonk, New York; IBM Corp.). The significance level was set at $p = .05$, two-tailed. Imputation was used to deal with random missing data to obtain the most accurate data set (Donders et al., 2006). We largely avoided the multiple comparison problem by performing the partial correlations only on a few electrophysiological variables of interest, predetermined in the independent pilot study.

First, the amount of children with an IAPF < 9 Hz, thereby supposedly displaying an overlap with the fixed 4 – 8 Hz theta-band, and the correlation between IAPF and theta were determined. Theta power and theta/beta power ratio were then correlated with the variables of interest (i.e., variables derived from the ADHD Rating Scale IV filled out by investigator and the neurocognitive tasks) while controlling for IAPF. Zero-order correlations were compared to correlations after keeping IAPF constant by determining whether a significant relation was revealed or abolished after controlling for IAPF, and by statistically comparing the correlation coefficients using a z-test. Pooled data for imputed data sets do not yield *p*-values. Therefore, for imputed data sets, correlations were reported on pooled data, while significance was determined based on the original data sets.

Results

Demographic and clinical characteristics

Forty-nine children were selected for EEG-measurement. For all children clinical information and scores on the ADHD Rating Scale IV were available. Six children were excluded due to inadequate EEG-signal quality. Another five children were excluded from the main analyses because a non-comparable EEG-system was used; these data were used for pilot analyses. Hence, for 38 children (10.5 ± 2.6 years, 84.2% boys) the relationship between ADHD Rating Scale IV rated by investigator and EEG data were analyzed. Six children were excluded from the treatment study, consequently lacking administration of the neurocognitive test-battery in these children. For the remaining 32 children (mean age 10.6 ± 2.2, 81.3% boys) neurocognitive measurements were available. An overview of the selection procedure is depicted in *Figure A1*, in the appendix of this chapter. Descriptive characteristics can be found in Table A1, in the appendix. Imputation of missing data was used for the SA-DOTS and VSS (3.12%) and the Time Reproduction task (6.25%).

Overlap between individual alpha-band and relative theta power

In line with our hypothesis, eight children (21%) showed an IAPF < 9 Hz, supposedly creating an overlap between the individual determined alpha-band and the conventionally defined theta-band (4 – 8 Hz). Consequently, a significant negative correlation was found between the IAPF and theta (r = -.412, p = .010) which

disappeared after excluding these eight children from analyses (r = -.280, p = .133). Eight additional children (another 21%) showed an IAPF of 9 Hz, potentially creating a slight overlap (see *Figure 1a*).

Partial correlations

Significant relationships were found between theta power and part of the ADHD symptoms (inattentive symptoms: r = .112, p = .505; hyperactive/impulsive symptoms: r = .344, p = .034; total symptoms: r = .315, p = .054). These became stronger after controlling for IAPF (inattentive symptoms: r = .272, p = .104; hyperactive/impulsive symptoms: r = .396, p = .015; total symptoms: r = .427, p = .008). Similarly, significant relationships between the theta/beta power ratio and part of the ADHD symptoms (inattentive symptoms: r = .212, p = .202; hyperactive/impulsive symptoms: r = .312, p = .057; total symptoms: r = .335, p = .040) became stronger after controlling for IAPF (inattentive symptoms: r = .307, p = .065; hyperactive/impulsive symptoms: r = .331, p = .045; total symptoms: r = .392, p = .017). The differences between the zero-order and IAPF-controlled correlations were non-significant. Also, no significant relationships were found between the theta power or the theta/beta power ratio and any of the neurocognitive measures with or without controlling for IAPF. Results can be found in Table A2 of the appendix.

Discussion

In this study a gradual reference framework was used by correlating theta power and the theta/beta power ratio with behavioral functioning in children with ADHD. Furthermore, it was investigated whether IAPF influenced this correlation by keeping IAPF variability constant. The hypotheses that led us to conduct this study were twofold; 1) theta power and theta/beta power ratio were expected to show a positive relationship with clinical symptoms were expected based on the robust finding of elevated theta power in children with ADHD with an inherent clinical symptom-level of inattention and hyperactivity/impulsivity; a similar expectation was suggested regarding deviation of accompanying neurocognitive ADHD-characteristics, 2) the IAPF was hypothesized to influence these relationships by showing a supposed overlap between individually determined alpha-band and fixed theta-band in part of the children, thereby potentially falsely overestimating theta power.

In line with a dichotomous difference between ADHD and controls found in previous studies (for meta-analysis, see Arns et al., 2013) and as expected, a positive relationship was found between theta/beta power ratio and the total and hyperactive/impulsive symptom score on the ADHD Rating Scale IV In addition, also expected, a positive relationship was found between theta power and hyperactive/impulsive symptoms. Twenty-one percent of the children in our study showed a supposed overlap between the individually based alpha-band and fixed theta-band. Consequently, IAPF and theta power correlated moderately. As hypothesized, all relationships between the theta power and theta/beta power ratio, and core-symptoms of ADHD became stronger when controlling for IAPF. However, the differences between zero-correlations and IAPF-controlled correlations were non-significant. Still, the relationship between theta power and total symptom score after controlling for IAPF changed from non-significant to a strong significant correlation. In contrast to what was expected, neurocognitive performance did not show any relationship with theta power or the theta/beta power ratio.

On symptomatic level, results confirmed our hypotheses; the theta power and theta/beta power ratio were related to core-symptoms of ADHD and controlling for IAPF influenced these relationships. The direction of the results however, was different from what would be expected based on literature. Lansbergen et al (2011a) found that a dichotomous difference between ADHD and controls was *lacking* when taking into account the IAPF. To come to this conclusion, the theta frequency-band in that study was determined using IAPF as anchor point (0.4*IAPF – 0.6*IAPF). A shift of IAPF however, does not necessarily imply a proportional shift of the other frequency-bands, among them the theta-band. Application of this method on the current example data sets showed that the theta-band in *Figure 1a* would become 3.5 – 5.2 Hz, resulting in an estimation of the theta-band based on the theta-band as well as an additional lower peak. The theta-band in *Figure 1b* would become 3.1 – 4.7 Hz, resulting in an underestimation of theta since not the entire theta-band would be covered by this new determined band. Although the results of Lansbergen and colleagues illustrated that the IAPFs differ enough from 10 Hz to shift the bands away from the dichotomous difference, the results do not necessarily imply an actual lack of the dichotomous difference from the 'normative' theta- and beta-band. The current study aimed at unraveling the influence of the IAPF-based alpha-band on the fixed theta-band of 4 – 8 Hz. By using a fixed theta-band comparable to the majority of previous studies (Arns et al., 2013), and an individual alpha-band comparable to

Lansbergen and colleagues, we were able to show that the relationship between the conventional theta power and theta/beta power ratio, and core-symptoms of ADHD became stronger when controlling for IAPF rather than eliminated.

The hypothesis of a relationship between theta power and theta/beta power ratio and neurocognitive results could not be confirmed by this study, which might be explained in different ways. Although neurocognitive deficits have been recognized in ADHD, without partitioning the neurocognitive heterogeneity within the group of children with ADHD (Nigg, 2005), the measures might not be sensitive enough to detect relationships such as with theta power and theta/beta power ratio. Furthermore, both neurocognitive and neurophysiological measurements are more vulnerable for transient state effects due to the short duration of measurement than a behavioral measurement, which is based on a significantly longer time period (Kendler & Neale, 2010). Consequently, transient state effects might be smallest in the confirmed behavioral hypotheses.

The interpretation of our findings should take into account a number of limitations. First, medication use has shown to have a large impact on the EEG activity in children with ADHD (Swartwood et al., 1998; Loo et al., 2004). The majority of the children in our sample used medication; yet, all children nevertheless displayed symptoms in the clinical range, meaning that medication-use did not diminish ADHD-symptoms sufficiently. Also, our sample size and hence the statistical power were relatively small. This prohibited analyses of neurocognitive subtypes as suggested in the literature (Nigg, 2005). To control the false alarm rate for the statistical inference, we a-priori chose a limited number of electrophysiological variables based on previous studies and our pilot-analysis. These choices restricted the analyses to one electrode, enlarging the potential influence of noise and disallowing topographical localization of the measures. The lack of a relationship between neurocognitive results and other measures questions whether causal claims can be made about different characteristics of ADHD; in particular the directionality and nature of relationship between core-symptoms, neurocognitive characteristics, and neurophysiology (Kendler & Neale, 2010). Simultaneous measurement of neurocognition and neurophysiology might give more insight as to whether these are part of a similar causal pathway; an important question that needs to be addressed in the future (Kendler & Neale, 2010). As a last remark, this study was performed under the assumption that findings can be captured within frequency-bands with independent functions. A more integrated

analysis will contribute to a fuller understanding of the underlying neurophysiology. In conclusion, this study confirmed the influence of IAPF on the conventional EEG measures in ADHD. Until now, resting-state EEG research in ADHD has been primarily focused on fixed theta- and beta-band; future research should expand to studying individualized frequency band patterns.

Appendix

Independent pilot study

To make an informed choice of analysis parameters and to limit the number of EEG variables, i.e., minimize multiple comparisons for the subsequent analysis, we used literature and a pilot analysis on independent data. These data came from children participating in the selection procedure from the same clinical trial, that were a-priori excluded from analysis due EEG-recording with a non-comparable EEG system (N = 5, all data available for N = 4). In these subjects EEG was recorded from 32 scalp electrodes placed according to the 10 – 20 system using the Acticap and BrainAmp system (Brain Products GmbH, Munich). The left mastoid (earlobe) was used as online reference, offline the data were referenced to linked mastoids (earlobes). Electrode Fpz was used as ground. Electrode impedance was kept below 10 kOhm. The sampling rate was set to 256 Hz.

Regarding theta power, the pilot results showed – in line with the literature (Boutros, Fraenkel & Feingold, 2005) – that relative rather than absolute theta power was more predictive. Relative power is less sensitive to individual variation (accounting for the variation in thickness and resistance of the skull). The analyses suggested no relationship between the behavioral measures and absolute or relative beta power, consistent with the ambiguous findings in the literature (Arns et al., 2013), although possibly also due to the small pilot sample size. Alpha activity is generally observed strongest in the visual/occipital regions when closing the eyes. To verify whether individualized alpha frequencies (IAPFs) could also be derived from the vertex, the method to derive the IAPFs (explained in *Electrophysiological procedure*, earlier in this chapter) was applied to occipital and vertex electrodes. The pilot data showed that it was possible to identify the IAPF at the vertex.

CONSORT flow diagram

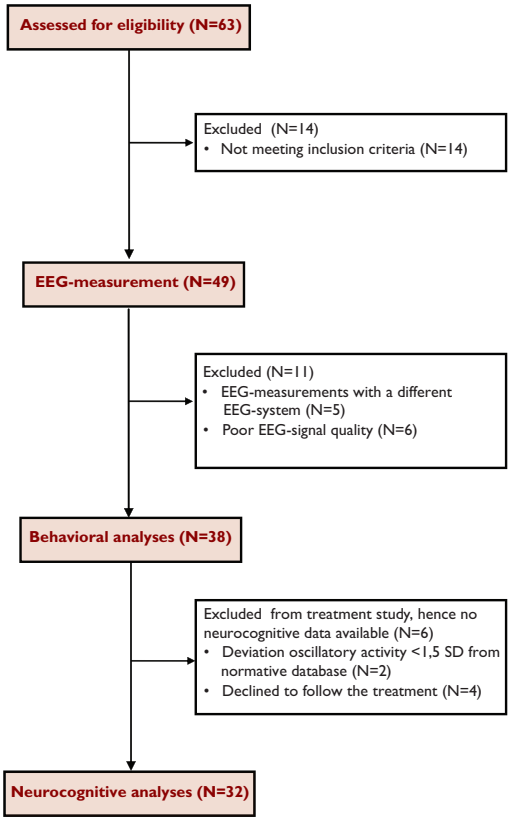


Figure A1. CONSORT flow diagram of study participants

Abbreviations: CONSORT: Consolidated Standards of Reporting Trials; N: number; EEG: electroencephalographic; SD: standard deviation.

Descriptive characteristics

Table A1. *Descriptive characteristics*

Descriptive characteristics	EEG analyses	
	Core-symptoms analyses (N = 38)	Neurocognitive analyses (N = 32)
Age, M (SD), y	10.5 ± 2.6	10.6 ± 2.2
Gender, N (%)		
male	32 (84.2)	26 (81.3)
Race, N (%)		
Caucasian	36 (94.7)	30 (93.8)
Black	2 (5.3)	2 (6.3)
Handedness, N (%)		
right	34 (89.5)	29 (90.6)
left	4 (10.5)	3 (9.4)
Full scale IQ, M (SD)	104.5 ± 17.1[×]	103.8 ± 15.9
Medication for ADHD, N (%)		
psychostimulants	21 (55.3)	18 (56.3)
atomoxetine	1 (2.6)	1 (3.1)
no medication	16 (42.1)	13 (40.6)
Melatonin, N (%)	8 (21.1)	7 (21.9)
ADHD subtype, N (%)		
combined	27 (71.1)	23 (71.9)
inattentive	10 (26.3)	8 (25.0)
hyperactive/impulsive	1 (2.6)	1 (3.1)
Comorbidity, N (%)		
oppositional defiant disorder	5 (13.2)	5 (15.6)
anxiety disorders	4 (10.5)	3 (9.4)
dyslexia	5 (13.2)	2 (6.3)
ADHD-RS, M (SD)		
total score	32.2 ± 9.2	32.2 ± 8.8
inattentive symptom score	18.3 ± 4.1	18.3 ± 4.2
hyperactive/impulsive symptom score	13.8 ± 7.0	13.9 ± 6.9

Note: [×] N is two points lower than the rest.

Abbreviations: EEG: electroencephalographic; N: number; M: mean; SD: standard deviation; y: years, IQ: Intelligent Quotient; ADHD-RS: ADHD Rating Scale IV.

Partial correlations

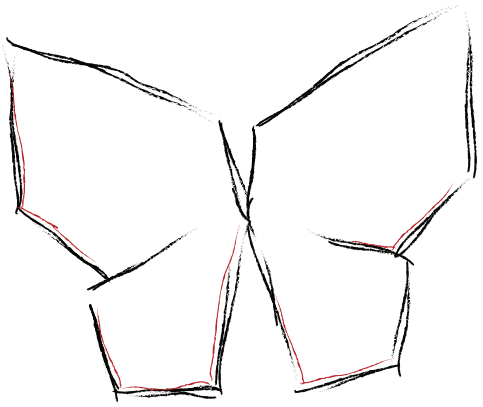
Table A2. *Partial correlations*

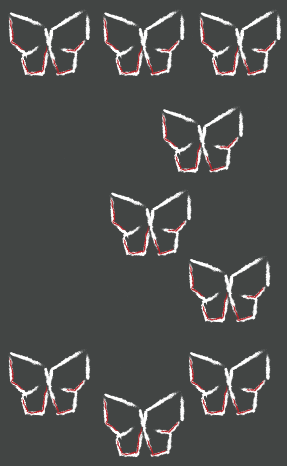
Test variables	No control IAPF		Control IAPF	
	Θ/β	Θ	Θ/β	Θ
ADHD-RS				
total symptoms	.335*	.315	.392*	.427**
inattentive symptoms	.212	.112	.307	.272
hyperactive/impulsive symptoms	.312	.344*	.331*	.396*
SA-DOTS ×				
mean response time	.046	-.007	.034	-.057
standard deviation of response time	-.105	-.060	-.126	-.133
number of hits	.121	-.010	.186	.165
number of correct rejections	.015	-.126	.052	-.009
VSS×				
number of correct trials	-.169	-.111	-.147	.003
number of identified targets	-.227	-.196	-.210	-.111
number of identified targets in correct order	-.121	-.051	-.095	.073
number of false alarms	.236	.210	.220	.125
Digit Span-WISC-III				
forward repetition of digits	-.085	-.075	-.052	.071
backward repetition of digits	-.027	.110	-.004	.212
RAVLT				
direct recalled words	.177	-.021	.171	-.052
delayed recalled words	-.065	-.162	-.057	-.141
Instrumental Learning task				
high reward % targets chosen in reward condition	.098	-.029	.116	.030
high reward % target chosen in neutral condition	.075	-.107	.088	-.067
reach learning criterion in reward condition	-.158	.105	-.154	.131
reach learning criterion in neutral condition	-.096	-.110	-.110	-.163
Time Production task				
mean deviation	.082	.019	.082	.020
standard deviation from mean deviation	-.002	-.075	.019	-.004
Time Reproduction task ×				
mean deviation	.055	.111	.044	.039
standard deviation from mean deviation	.025	.110	.014	.049

* = $p \leq .05$, ** = $p \leq .01$.

Note: ×the *r* is displayed for pooled results after imputation.

Abbreviations: IAPF: individual alpha peak frequency; Θ: relative theta power; Θ/β: theta/beta power ratio; ADHD-RS: ADHD Rating Scale IV; SA-DOTS: Sustained Attention Dots task; VSS: Visuospatial Sequencing; Digit Span-WISC-III: Digit Span from the Wechsler Intelligence Scale for Children-III; RAVLT: Rey Auditory-Verbal Learning Test.





A randomized placebo-controlled trial of EEG-neurofeedback in children with Attention-Deficit/ Hyperactivity Disorder

A double-blind, randomized, placebo-controlled study was designed to assess the efficacy and safety of EEG- neurofeedback in children with ADHD. The study started in August 2008 and ended in July 2012 and was conducted at Karakter Child and Adolescent Psychiatry University Centre in Nijmegen, the Netherlands.

Forty-one children (8 – 15 years old) with a *DSM-IV-TR* diagnosis of ADHD were randomly assigned to EEG-neurofeedback or placebo-neurofeedback treatment for 30 sessions, given as 2 sessions per week. The children were stratified by age, electrophysiological state of arousal, and medication use. Everyone involved in the study, except the neurofeedback therapist and the principal investigator, was blinded to treatment assignment. The primary outcome was the severity of ADHD behavioral core-symptoms on the ADHD Rating Scale IV, scored at baseline, during treatment, and at study end. Clinical improvement as measured by the Clinical Global Impressions-Improvement (CGI-I) scale was a secondary outcome.

While ADHD core-symptoms improved over time in both groups ($p < .001$), there was no significant treatment effect, i.e., group x time interaction ($F(1,39) = 0.36$, $p = .554$); the same was true for clinical improvement as measured by the CGI-I scale ($p = .092$). No clinically relevant side effects were observed. Among the children and their parents, guessing treatment assignment was not better than chance level ($p = .224$ for children, $p = .643$ for parents). In this study, EEG-neurofeedback was not superior to placebo-neurofeedback in improving ADHD symptoms in children with ADHD.

Based on

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*** joint last authorship**

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Introduction

A substantial proportion of children with ADHD fail to respond favorably to the first-line treatment medication (Brown et al., 2005). Indications that long-term use of medication affects growth, neural functioning and the cardiovascular system (Graham et al., 2011) and the absence of evidence for long-term efficacy of medication for ADHD (Spencer et al., 2002; van de Loo-Neus, Rommelse, & Buitelaar, 2011) points to the need for non-pharmacological treatment options.

Electroencephalographic (EEG) neurofeedback is such an option. With EEG-neurofeedback, the hypothesis is that voluntary modulation of specific brain activity patterns can be learned by operant learning strategies via provision of continuous real-time feedback, i.e., positive reinforcement when changes are made in the desired direction, through visual and/or acoustic signals representing the brain activity (Gevensleben et al., 2012). Most often, the aim of EEG-neurofeedback is to increase beta activity (or sensorimotor rhythm [SMR], 12 – 15 Hz over the motor cortex), while suppressing theta activity (Monastra et al., 2005). This goal is based on the observation that slow-wave activity (primarily theta [4 – 7 Hz]) is increased and fast-wave activity (beta [12 – 30 Hz]) is decreased in most patients with ADHD (for review, see Barry et al, 2003). Different EEG-neurofeedback treatment protocols are in use. For example, a predetermined protocol (mostly a theta/beta protocol) can be used that does not necessarily require pre-treatment EEG analysis to assess the individual resting-state EEG. Alternatively, a pre-treatment quantitative electroencephalogram (qEEG) analysis is performed, and, after comparison of findings with those from a normative database, a personalized treatment protocol focusing on the resting-state EEG features of that individual is drawn up. The first method has the advantage that a standardized treatment protocol is used, and the second has the advantage that treatment is personalized and targeted to the specific EEG deviations of that individual.

Recent reviews are reserved about the efficacy of EEG-neurofeedback in children with ADHD, despite the finding of medium to large effect sizes (ESs), mainly because of methodological shortcomings of the studies (Gevensleben et al., 2012; Lofthouse et al., 2012; Lofthouse, Arnold, & Hurt, 2012; Moriyama et al., 2012). Although the most recent published studies have more robust methodological designs, only 3 of more than 20 published randomized controlled trials (RCTs) included a placebo

condition (Perreau-Linck et al., 2010; Lansbergen et al. 2011b; Arnold et al., 2012). A systematic review and meta-analysis of RCTs of non-pharmacological interventions in children with ADHD reported non-significant results for the blinded rating of symptoms (p = .07) (Sonuga-Barke et al., 2013). Moreover, none of the three published placebo-controlled trials showed EEG-neurofeedback to be superior to placebo-neurofeedback. The question whether EEG-neurofeedback is a safe treatment has still to be addressed. As far as we know, our pilot study was the first to systematically monitor safety (Lansbergen et al., 2011b).

At the time our study was designed and begun, EEG-neurofeedback was thought to be a promising treatment for ADHD. So, we expected significant improvement of ADHD symptoms after EEG-neurofeedback compared to placebo-neurofeedback.

This current study is a valuable addition to the existing literature because of a larger study sample, the use of qualified neurofeedback therapists, the double-blind design and the inclusion of only participants with a deviant pre-treatment EEG. The latter made it possible to apply personalized EEG-neurofeedback.

In sum, the present, double-blind, randomized, placebo-controlled trial was designed to critically evaluate the efficacy in reducing ADHD behavioral core-symptoms and the safety of EEG-neurofeedback in children with ADHD. The study was registered on ClinicalTrials.gov (identifier: NCT00723684).

Methods

Trial design

This study started as a triple-blind, placebo-controlled treatment trial, with stratified randomization for age (younger vs. older than 12 years), electrophysiological state of arousal (hyper-arousal vs. hypo-arousal), and use of medication (with vs. without medication). After our pilot study (Lansbergen et al., 2011b), we made 2 changes: (1) Automatically adjusted reward thresholds in the EEG-neurofeedback condition were changed into manually adjusted reward thresholds, with the consequence that the neurofeedback therapist was no longer blinded to treatment assignment; note that the children, their parents and teachers, and the raters were still blinded to

treatment assignment. (2) Active learning strategies were introduced, so that children could integrate the learned strategies into daily life.

Children with ADHD were stratified and then randomly assigned in a double-blind manner (1:1 assignment using random block sizes of two) to either EEG-neurofeedback or placebo-neurofeedback (treatments to be given twice per week for a total of 30 sessions). The assignment was done by the principal investigator, who was not involved in data collection.

All people involved in the study were blinded to treatment assignment, with the exception of the neurofeedback therapist and the principal investigator, who were not involved in data collection, data entry, and data analysis. Since both participants and raters were still blinded to treatment assignment, this study was labeled as double-blind.

Participants

Children (aged 8 – 15 years old) were included if 1) they had been clinically diagnosed with ADHD according to the *Diagnostic and Statistical Manual of Mental Disorders (4th ed., text rev. [DSM-IV-TR]*, American Psychiatric Association, 2000), 2) they had an (estimated) full-scale Intelligence Quotient (IQ) of at least 80, 3) their qEEG, a technique to produce a visual map of different frequencies and locations of a signal measured from the brain using EEG, deviated at least 1.5 standard deviations (SDs) from normative data, 4) they did not use psychoactive drugs, or they used a stable dose of psychostimulants or atomoxetine, and 5) there was room for improvement, defined as a minimum score of 2 on a 4-point Likert scale for at least 6 items of the ADHD Rating Scale IV (ADHD-RS) (Zhang et al., 2005). Children were excluded if they 1) were involved in individual or group psychotherapy, 2) used medication other than psychostimulants or atomoxetine, 3) had a comorbid disorder other than oppositional defiant disorder or any anxiety disorder, 4) had a neurological disorder and/or a cardiovascular disease, 5) participated in another clinical trial at the same time, 6) had received EEG-neurofeedback in the past, or 7) used alcohol or drugs.

Psychostimulants or atomoxetine were permitted because the majority of severely affected children with ADHD in the Netherlands uses medication. The discontinuation of medication would have been ethically questionable due to the consequence of

withholding an evidence-based treatment. Moreover, the exclusion of children on medication would have limited the generalizability of findings.

A psychologist or doctor screened potential participants for eligibility by asking their parents a number of questions over the telephone. Current ADHD symptoms and other psychiatric symptoms were checked. The Dutch version of the Autism Screening Questionnaire (ASQ) (Berument et al., 1999) was used to screen for autism spectrum disorders. Children who screened positive for ADHD symptoms underwent an extensive diagnostic procedure, including the ADHD-RS and a developmental and psychiatric interview with a child and adolescent psychiatrist, who confirmed the diagnosis on the basis of the findings. The presence of co-morbid disorders was assessed with the Diagnostic Interview Schedule for Children (Shaffer et al., 2000; Steenhuis et al., 2009). General functioning was measured using the Children's Global Assessment Scale (CGAS) (Shaffer et al., 1983), and the severity of ADHD was assessed with the Clinical Global Impressions-Severity Scale (Guy, 1976). If intelligence had not been assessed in the past 1.5 years, 2 subtests of the Wechsler Intelligence Scale for Children 3rd Edition (WISC-III) were administered (i.e., Vocabulary and Block Design) to estimate intelligence (Wechsler, 1949, 1989, 1991). Finally, a 20-minutes (min) EEG was recorded to assess whether the child's qEEG deviated from the NeuroGuide normative database (Thatcher, 1998).

As predetermined, recruitment started in August 2008 and ended in May 2012. Children were recruited from among referrals to Karakter Child and Adolescent Psychiatry University Centre in Nijmegen, the Netherlands, and from responders to advertisements in the magazine "Balans" (the Dutch association of parents with children with learning or behavioral disorders). The study was approved by the Dutch Central Medical Ethics Committee (www.ccmo.nl) and conducted in accordance with the Declaration of Helsinki. All parents and all children older than 12 years of age gave their written informed consent before participation; children younger than 12 years of age gave oral assent. Travel expenses were partially reimbursed. All children received a gift certificate worth 10 euro and a small present during evaluation.

Sample size was calculated for the primary outcome, on the basis of the following considerations. Double-blind, placebo-controlled trials have shown an ES of 0.6 or more for the first-line treatment of ADHD with medication (Michelson et al., 2002;

Faraone & Buitelaar, 2010). Pilot open-label studies with EEG-neurofeedback also report an ES of about 0.6 (Fuchs et al., 2003). With an alpha error of .05, we calculated that a sample of 60 children in the EEG-neurofeedback arm and 60 in the placebo-neurofeedback arm would enable us to detect treatment effects with an ES of 0.5 and a power of 80%.

Interventions

The *Neurofeedback Instituut Nederland B.V.* provided the EEG-neurofeedback and placebo-neurofeedback training. Individualized EEG-neurofeedback protocols based on visual inspection of the raw EEG and qEEG were used for EEG-neurofeedback training.

To determine whether EEG data deviated from the NeuroGuide database, a minimum of 10 minutes of clean raw EEG per condition (i.e., eyes-open and eyes-closed) was acquired. The aim of the EEG-neurofeedback training was to normalize power within individually determined frequency bands and electrode sites by receiving feedback on their real-time EEG signal. During the 45-min sessions, after preparation, the children watched a film for 20 minutes while sitting quietly on a chair in an "active focusing state" with eyes open. They were instructed to try to self-regulate their brain activity by receiving positive feedback. Positive feedback was provided by brightening the computer screen and by presenting auditory tones. Most children in the EEG-neurofeedback group were trained to increase the presence of the sensorimotor rhythm or low-beta activity while simultaneously suppressing the presence of theta activity, meaning that when the production of low-beta activity remained above threshold and/or the theta/beta power ratio remained below threshold positive feedback was given. Reward threshold levels were manually adjusted to 80% for eacht training target (i.e. frequency-band and/or location). Consequently, the amount of reward remained at about the same level across sessions and across groups. An identical procedure was provided in the placebo-neurofeedback group, except that children in the placebo-neurofeedback group received feedback on a simulated EEG signal, consisting of a random signal similar to real EEG. BrainMaster Atlantis hardware and software were used to provide both training modalities (BrainMaster Technologies; Bedford, Ohio). Feedback on real EEG and simulated EEG signals seemed similar, in experiences in an earlier study (Logemann et al., 2010) and in our pilot study (Lansbergen et al., 2011b), such that participants did not know whether they had received real or placebo-neurofeedback.

At each session the child was given a sticker, and 30 stickers were rewarded, with a small present given at the last appointment.

Recruitment and assessments were performed at Karakter Child and Adolescent Psychiatry University Centre in Nijmegen, the Netherlands.

Outcomes

Efficacy measures

The primary endpoint was efficacy, measured as the difference before and after training of the total severity of inattentive and hyperactive/impulsive symptoms of ADHD according to the ADHD-RS, scored by the investigator in an interview with the parents at baseline; after 6, 10, and 20 sessions, and at study end, using a 4-point Likert scale (0 = never occurs, 1 = occurs sometimes, 2 = occurs often, 3 = occurs very often). Additional analyses were performed for teacher-reported symptoms conducted on the ADHD-RS at baseline, after 10 and 20 sessions, and at study end. The Clinical Global Impressions-Improvement scale (CGI-I) (Guy, 1976), a widely used scale to evaluate clinical effects in intervention studies, was administered in a final interview by the investigator and was used as an additional outcome measure. The CGI-I consists of a single item 7-point scale (1 = very much improved, 2 = much improved, 3 = minimally improved, 4 = no change, 5 = minimally worse, 6 = much worse, 7 = very much worse). Responders were defined as children who were rated as very much improved or much improved. Another outcome measurement was the global improvement in functioning, which was assessed as the difference between baseline and end-of-study scores on the CGAS (scale 0–100, with 0 = most affected global functioning and 100 = best global functioning).

Safety measures

Potential adverse effects of the intervention were measured with the Pittsburgh Side Effects Rating Scale (PSERS), a scale often used in drug treatment studies (Pelham et al., 1993; Sandler & Bodfish, 2008), using the total score for all items (4-point scale: 0 = not present, 1 = mild, 2 = moderate, 3 = severe) at baseline, in between, and at study end (Pelham et al., 1993; Sandler & Bodfish, 2008). For this study, three items were added to the original scale, i.e., epileptic seizures, nausea, and feeling agitated. Side effects on sleep quality were assessed by summing the scores of 14 insomnia items on the Dutch version of the Sleep Disorders Questionnaire (SDQ) (Sweere,

1998) (5-point scale: 0 = never, 1 = rarely, 2 = sometimes, 3 = usually, 4 = always) at baseline and at study end.

Feasibility outcome

Parents and children were asked about their experience with the training and whether they thought the child had received EEG-neurofeedback or placebo-neurofeedback training.

Statistical methods

Statistical analyses were performed with the IBM SPSS Statistics, version 20.0 (Armonk, New York; IBM Corp.). For each parameter, mean and standard deviation (SD) were computed. The significance level was set at $p = .05$ (two-tailed). Repeated-measures analyses of variance, with time as within-subjects factor and group (EEG-neurofeedback vs. placebo-neurofeedback) as between-subjects factor were performed separately for the sum of inattentive symptoms, the sum of hyperactive/impulsive symptoms, the sum of all symptoms on the ADHD-RS, the total sum of adverse events (PSERS), the total sum of sleep problems as rated by the SDQ, and the CGAS. For the analysis of the ADHD-RS scores, as rated by the investigator, the within-subjects factor time had five levels (i.e., baseline, after 6, 10, and 20 sessions, and at study end). For the analysis of the teacher-rated ADHD-RS, the PSERS, the SDQ, and the CGAS, the within-subjects factor time had two levels (i.e., baseline and study end). Differences between the groups on the CGI-I at study end were tested by a t-test. Post-hoc analysis of covariance was performed with the covariates gender, age, medication, and electrophysiological state of arousal.

In preliminary analyses, the efficacy and safety of the EEG-neurofeedback treatment of the first 8 patients (automatic thresholding, no implementation of active learning strategies) and of another 14 patients (manual thresholding and implementation of active learning strategies) were assessed. As there were no differences in efficacy and safety between these two groups, the data of the two series of EEG-neurofeedback were summed, and results for the whole sample are reported.

Results

Demographic and clinical characteristics

In total, 63 children and their parents were eligible for the study and were examined clinically (*Figure 1*). Twenty-two subjects were excluded. One child withdrew during selection. Four children were included but not enrolled; just before training started, the parents and/or child decided to withdraw because it was difficult fitting the sessions into their daily schedule. Seventeen children either did not meet the inclusion criteria or did meet exclusion criteria and were excluded for the following reasons: no room for improvement (N = 6), no deviant EEG (N = 3), epileptic activity on EEG (N = 1), comorbid Gilles de la Tourette (N = 1), no ADHD (but dysthymic disorder) (N = 1), too great a burden to participate (N = 1), unstable use of ADHD-medication (N = 1) and a combination of criteria (N = 3) (above the cut-off score on the SCQ, unstable use of ADHD-medication and too great a burden to participate [N = 2], above cut-off score on the SCQ and no room for improvement [N = 1]).

Thus, 41 children participated in the study. The mean (SD) age of the sample was 10.62 (2.25) and there were 34 boys; 22 children were allocated to the EEG-neurofeedback group (8 in the pilot study, 14 post-pilot study), and 19 were allocated to the placebo-neurofeedback group. As expected as a result of randomization, no significant differences were found between the two groups on baseline characteristics (Table 1). All 41 children completed training. Two children unintentionally changed the dosage of their medication during the treatment phase (one increased the dosage of the psychostimulant, and the other incidentally introduced drug-free weekends and holidays).

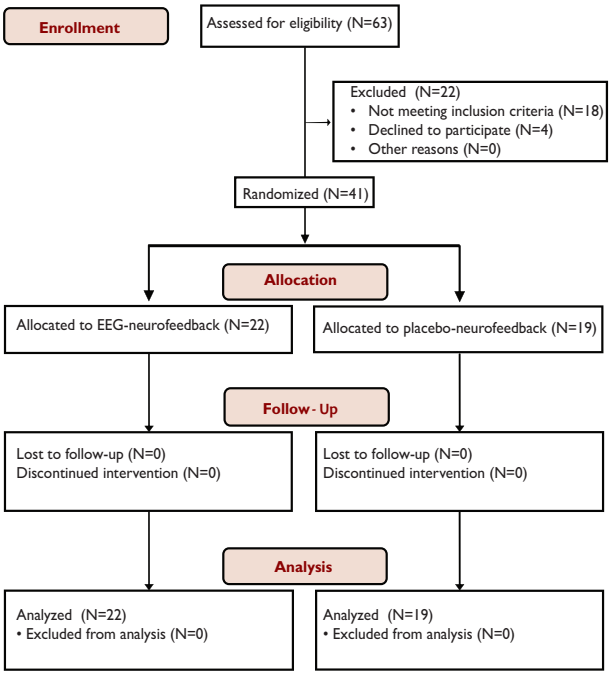


Figure 1. CONSORT flow diagram of study participants

Abbreviations: CONSORT: Consolidated Standards of Reporting Trials; N: number; EEG: electroencephalographic.

Table 1. Descriptive baseline demographic and clinical characteristics by treatment group (N = 41)

Characteristics	EEG-neurofeedback (N = 22)	Placebo-neurofeedback (N = 19)	Analysis t, χ^2, *p*-value
Age, M (SD), y	10.5 (2.2)	10.7 (2.3)	*p* = .734
Gender, N (%)			*p* = 1.000
male	19 (86.4)	15 (78.9)	
female	3 (13.6)	4 (21.1)	
Race, N (%)			*p* = 1.000
Caucasian	20 (91)	18 (95)	
Black	2 (9)	1 (5)	
Full-scale IQ, M (SD)	108.8 (19.4)	102.1 (12.2)	*p* = .205
Medication for ADHD, N (%)			*p* = .726
psychostimulants	11 (50)	14 (73.7)	
atomoxetine	1 (4.5)	0 (0)	
no medication	10 (45.5)	5 (26.3)	
EEG arousal, N (%)			*p* =.513
hypo-aroused	19 (86.4)	14 (73.7)	
hyper-aroused	3 (13.6)	5 (26.3)	
ADHD subtype, N (%)			*p* =.543
combined	17 (77.3)	13 (68.4)	
inattentive	4 (18.2)	5 (26.3)	
hyperactive/impulsive	1 (4.5)	1 (5.3)	

Table 1. Continued

Characteristics	EEG-neurofeedback (N = 22)	Placebo-neurofeedback (N = 19)	Analysis t, χ^2, *p*-value
Comorbidity, N (%)			
oppositional defiant disorder	5 (22.7)	1 (5.3)	*p* = .191
anxiety disorders	3 (13.6)	2 (10.5)	*p* = 1.000
dyslexia	2 (9)	3 (15.8)	*p* = .649
ADHD-RS-INV, M (SD)			
total symptoms	30.6 (7.5)	32.0 (9.6)	*p* = .601
inattentive symptoms	17.0 (5.1)	18.2 (3.4)	*p* = .369
hyperactive/impulsive symptoms	13.6 (5.5)	13.8 (7.9)	*p* = .942
ADHD-RS-Teacher, M (SD)			
total symptoms	23.6 (14.8)	25.7 (12.8)	*p* = .639
inattentive symptoms	13.1 (7.5)	13.9 (6.2)	*p* = .712
hyperactive/impulsive symptoms	10.6 (8.4)	11.8 (8.2)	*p* = .632
CGI-S, N (%)			*p* = .405
3- mildly ill	3 (13.6)	0 (0)	
4- moderately ill	12 (54.5)	11 (57.9)	
5- markedly ill	7 (31.8)	8 (42.1)	
CGAS, M (SD)	51.3 (6.6)	51.6 (5.6)	*p* = .703

Abbreviations: EEG: electroencephalographic; N: number; *t*: independent sample t-test; χ^2: chi-square test; *p*-value: probability value; M: mean; SD: standard deviation; y: years; IQ: Intelligence Quotient; ADHD-RS: ADHD Rating Scale IV; INV: Investigator; CGI-S scale: Clinical Global-Impressions Severity scale; CGAS: Children's Global Assessment Scale.

Efficacy outcome

Table 2 presents detailed statistical results for all study measures by treatment group.

ADHD Rating Scale IV as rated by the investigator

ADHD symptoms decreased over time ($F(1,39) = 26.56$, $p < .001$) to a similar extent in both groups and there was no group x time interaction effect ($F(1,39) = 0.36$, $p = .554$) (*Figure 2*). Similar results were observed when the inattentive and hyperactive/impulsive scores were analyzed separately.

ADHD Rating Scale IV as rated by the teacher

As nine teacher questionnaires were missing for the end-of-study assessment, last observation carrier forward (LOCF) data were used, except for two end-of-study measurements for which a baseline measurement was the only data present. Teacher-rated ADHD symptoms decreased significantly over time ($F(1,37) = 13.54$, $p = .001$), without a difference between groups ($F(1,37) = 0.45$, $p = .509$). Similar results were obtained for the inattentive and hyperactive/impulsive scores.

Table 2. Results for all study outcomes by treatment group (N = 41)

Measurement	EEG-neurofeedback[a]		Placebo-neurofeedback[a]		Analyses	
	Baseline M (SD)	Study end M (SD)	Baseline M (SD)	Study end M (SD)	Time-effect *F*, *p*	Group x time-effect *F*, *p*
ADHD-RS-INV					*F*(1,39)	*F*(1,39)
total symptoms	30.6 (7.5)	23.4 (9.5)	32.0 (9.6)	26.3 (7.2)	26.56, $p < .001$	0.36, $p = .554$
inattentive symptoms	17.0 (5.1)	13.2 (6.0)	18.2 (3.4)	13.8 (3.1)	27.17, $p < .001$	0.17, $p = .682$
hyperactive/impulsive symptoms	13.6 (5.5)	10.2 (5.3)	13.8 (7.9)	12.5 (6.3)	10.80, $p = .002$	2.26, $p = .141$
ADHD-RS-T					*F*(1,37)	*F*(1,37)
total symptoms	23.6 (14.8)	19.3 (11.4)	25.2 (12.5)	18.9 (10.2)	13.54, $p = .001$	0.45, $p = .509$
inattentive symptoms	13.1 (7.5)	11.3 (5.7)	13.4 (5.9)	11.0 (4.8)	7.63, $p = .009$	0.25, $p = .624$
hyperactive/impulsive symptoms	10.6 (8.4)	8.0 (7.0)	11.8 (8.3)	8.0 (6.6)	15.74, $p < .001$	0.53, $p = .473$
CGI-I[b]		3.2 (0.8)		3.6 (0.5)		$p = .092$
CGAS[b]	51.3(6.6)	58.1 (9.1)	51.6 (5.6)	54.8 (4.5)	*F*(1,38) 15.47, $p < .001$	*F*(1,38) 1,96, $p = .169$
SDQ	25.3 (8.3)	24.0 (7.0)	26.3 (6.3)	24.9 (9.2)	*F*(1,37) 5.42, $p = .025$	*F*(1,37) 0.05, $p = .818$
PSERS	5.5 (5.5)	4.1 (4.3)	5.6 (4.9)	3.9 (4.2)	*F*(1,39) 6.30, $p = .016$	*F*(1,39) 0.10, $p = .754$

Note: [a] Mean and standard deviation (in parentheses) are given for each parameter at baseline and study end. [b] Reduced scores reflect improvement, except for the CGI and CGAS.

Abbreviations: M: mean; SD: standard deviation; *p*: probability value; ADHD-RS: ADHD Rating Scale IV; -INV: rated by the investigator; -T: rated by the teacher; CGI-I: Clinical Global Impressions-Improvement scale; CGAS: Children's Global Assessment Scale; SDQ: Sleep Disorders Questionnaire; PSERS: Pittsburgh Side Effects Rating Scale.

Clinical Global Impressions – Improvement

On the CGI-I scale, 4 of 22 children (18%) in the EEG-neurofeedback group were rated as 'much improved', 9 of 22 (41%) in the EEG-neurofeedback group and 8 of 19 (42%) in the placebo-neurofeedback group were rated as 'minimally improved', and 9 of 22 (41%) in the EEG-neurofeedback group and 11 of 19 (58%) in the placebo-neurofeedback group were rated as unchanged at the end of the study. The differences between the groups were not significant (p = .092). None of the children deteriorated.

Children's Global Assessment Scale

One end-of-study value was missing in the EEG-neurofeedback group. The CGAS score increased significantly over time ($F(1,38)$ = 15.47, p < .001), but increased similarly in the two groups ($F(1,38)$ = 1.96, p = .169).

Safety outcomes

Adapted Sleep Disorders Questionnaire

Two end-of-study scores were missing in the placebo-neurofeedback group. Total sleep problems decreased significantly over time ($F(1,37)$ = 5.42, p = .025), but similarly in the two groups ($F(1,37)$ = 0.05, p = .818).

Adapted Pittsburgh Side Effects Rating Scale

Two values were missing in the EEG-neurofeedback group; the LOCF method was used for the missing data. The total number of adverse events decreased significantly over time ($F(1,39)$ = 6.30, p = .016) and decreased similarly in the two groups ($F(1,39)$ = 0.10, p = .754).

Post-hoc analyses

Post-hoc analyses with the covariates age, gender, medication use, and state of electrophysiological arousal did not reveal any significant treatment effect (i.e., group by time interaction) for any outcome. After correction, almost all significant results became non-significant, except for the effect of time on the CGAS, which changed to a marginally significant level ($F(1,34)$ =3.48, p = .071).

Feasibility examination

Among the children, 10 of 41 (24%) correctly guessed which treatment they had received, 13 of 41 (32%) guessed incorrectly, and 10 of 41 (24%) did not know; data were missing for 8 of 41 (20%) children. Among the parents, 14 of 41 (34%) guessed the treatment assignment correctly, 19 of 41 guessed incorrectly (46%), and 6 of 41 did not know (15%); data were missing for 2 of 41 (5%) parents. Fisher exact tests showed that the children and their parents did not guess treatment assignment significantly better than chance level (p = .224 for children, p = .643 for parents).

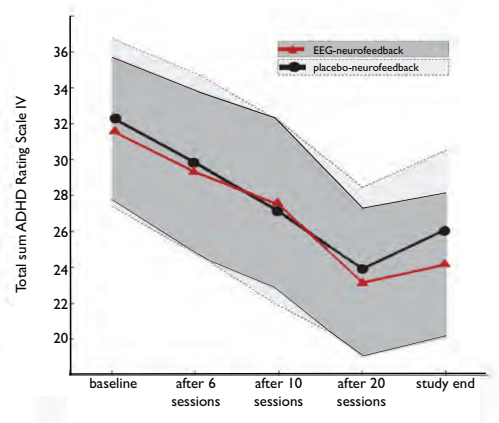


Figure 2. Mean total summed score and 95% confidence intervals for the ADHD Rating Scale IV over time as rated by the investigator and shown by treatment group

Discussion

This study examined the safety and efficacy of EEG-neurofeedback treatment for core-symptoms in children with ADHD, using a double-blind, randomized, placebo-controlled design with blinded participants and raters. Treatment assignment was not guessed better than chance level. EEG-neurofeedback was not superior to placebo-neurofeedback in affecting ADHD symptoms or other secondary efficacy outcomes. The intervention was safe as no adverse effects were reported. Post-hoc analyses with the covariates age, gender, medication, and electrophysiological state of arousal did not lead to any significant results compared to the main analyses. These findings are in line with those of our previous feasibility pilot study (Lansbergen et al., 2011b) and two recently published placebo-controlled EEG-neurofeedback studies (Perreau-

Linck et al., 2010; Arnold et al., 2012). Moreover, a recent systematic review and meta-analysis of randomized controlled trials of non-pharmacological interventions in children with ADHD concluded that the significant effect size of unblinded ratings could not have been replicated if blinded ratings were used (meta-analysis of seven open-label and one triple-blind EEG-neurofeedback studies) (Sonuga-Barke et al., 2013). Thus, it seems that methodologically sound studies do not confirm the efficacy of EEG-neurofeedback in children with ADHD.

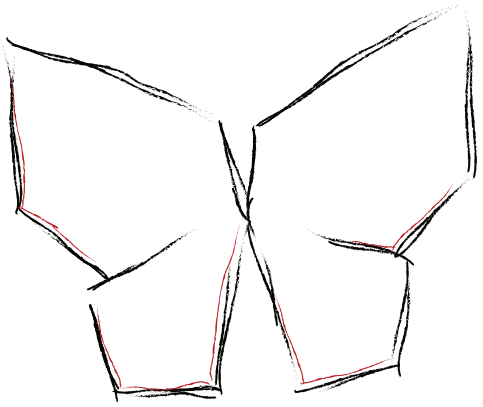
Changing from automatic to manual thresholds did not result in larger effects for EEG-neurofeedback, nor did the addition of active learning strategies. Making passive learning active by adopting learning strategies is hypothesized to be an important aspect of the working mechanism of EEG-neurofeedback (Gevensleben et al., 2012). Our findings did not support this hypothesis.

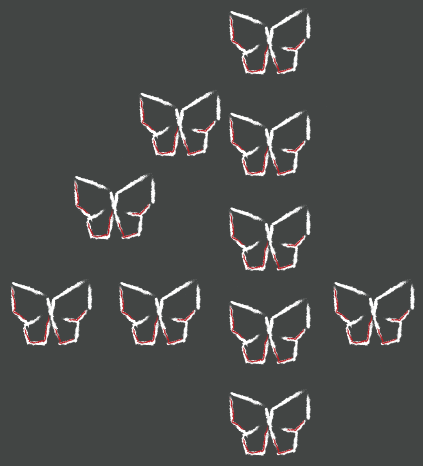
Unfortunately, we were unable to recruit a sufficient number of participants to meet our planned sample size. Post-hoc, our sample had 80% power to detect a treatment effect of 0.90. However, since there was virtually no difference between the effect of EEG-neurofeedback and placebo-neurofeedback in the smaller sample, it is unlikely that our negative results were due to limited statistical power.

The study was carefully designed to tackle the methodological shortcomings of previous studies, resulting in a randomized placebo-controlled trial with blinded participants and raters, an extended selection procedure, and several behavior and safety evaluations of both interventions. Conducting such study has drawbacks. First, the 50% chance of receiving placebo-neurofeedback treatment probably adversely influenced recruitment. During our entire clinical trial, patients with ADHD had access to EEG-neurofeedback in the general clinical practice without the risk of being assigned to placebo-neurofeedback and treatment costs were fully reimbursed by health insurance companies. Another potential limitation is the change from a triple-blind to a double-blind design (which means that the neurofeedback therapist was no longer blinded); however, participants and raters were still blinded to treatment assignment. The use of medication by most participants may have influenced the ability to detect a significant effect of EEG-neurofeedback. At this time, follow-up data are not available yet; we plan to re-assess all participants after six months and will describe these findings in a

separate report. Last, because most children were white, the generalizability of findings to other races cannot readily be assumed.

In conclusion, our results seriously question claims that EEG-neurofeedback is an effective treatment for children with ADHD. Further research with more participants is needed to determine whether this traditional form of neurofeedback is effective in particular patient subgroups.





Does EEG-neurofeedback improve neurocognitive functioning in children with Attention-Deficit/ Hyperactivity Disorder? A systematic review and a double-blind placebo-controlled study

The number of placebo-controlled randomized studies relating to EEG-neurofeedback and its effect on neurocognition in ADHD is limited. For this reason, a double-blind, randomized, placebo-controlled study was designed to assess the effects of EEG-neurofeedback on neurocognitive functioning in children with attention-deficit/hyperactivity disorder (ADHD), and a systematic review on this topic was performed.

Forty-one children (8 – 15 years old) with a *DSM-IV-TR* diagnosis of ADHD were randomly allocated to EEG-neurofeedback or placebo-neurofeedback treatment for 30 sessions, twice a week. Children were stratified by age, electrophysiological state of arousal, and medication use. Neurocognitive tests measuring executive functioning, attention, reward-related processes, and timing were administered before and after treatment. Researchers, teachers, children, and their parents, with the exception of the neurofeedback-therapist, were all blinded to treatment assignment. Outcome measures were the changes in neurocognitive performance before and after treatment. No significant treatment effect on any of the neurocognitive variables was found. A systematic review of the current literature also did not find any systematic beneficial effect of EEG-neurofeedback on neurocognitive functioning.

Overall, the existing literature and this study fail to support any benefit of neurofeedback on neurocognitive functioning in ADHD, possibly due to small sample sizes and other study limitations.

Based on
Vollebregt*, M.A.*, van Dongen-Boomsma, M.*, Slaats-Willemse, D., & Buitelaar, J.K.
*** joint first authorship**

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Introduction

ADHD is the most common childhood mental disorder, affecting about 5% of all children worldwide (Polanczyk et al., 2007) with an increasing prevalence over the last decade (Getahun et al., 2013). ADHD affects children's personal development substantially and is associated with impairments in social and emotional development, and poor academic and vocational outcomes (Wehmeier, Schacht, & Barkley, 2010). Consequently, the substantial burden on families and society in general is notable (Biederman, 2005; Biederman et al., 2012). Because of the severity and long-term nature of the impairments associated with ADHD, efforts have been made to understand the underlying deficits and identify effective treatments for ADHD.

ADHD & neurocognitive dysfunctions

Neurocognitive models of ADHD have attempted to explain the behavioral symptoms in underlying impairments in executive functions (EFs), attention regulation, reward-related processes, and timing. Associations between ADHD and EFs are found in domains of response inhibition, vigilance, working memory, and planning (Martinussen et al., 2005; Willcutt et al., 2005). ADHD-related attention problems are described as weak performances in selective and sustained attention, and attention shifting tasks (Weissman et al., 2012). Studies on reward-related processes in ADHD indicate a preference for small immediate rewards over later larger rewards (for review see Sonuga-Barke et al., 2008). Finally, timing deficits have consistently been found in subjects with ADHD in three major domains, i.e., motor timing, perceptual timing, and temporal foresight (for review see Noreika, Falter, & Rubia, 2013). Differentiation could be made between timing deficits and delay deficits (Sonuga-Barke, Bitsakou, & Thompson, 2010; de Zeeuw et al., 2012).

ADHD & EEG-neurofeedback

Concerns about the safety and long term efficacy of first-line treatment medication in ADHD have led to interest in developing alternative non-pharmacological treatment approaches.

EEG-neurofeedback is based on the rationale that voluntary modulation of specific brain activity patterns can be learned by operant learning strategies. In other words,

by providing continuous real time feedback, i.e., positive reinforcement when changes are made in the desired direction, the self-regulation of ongoing neuronal oscillations in one or more frequency-bands can be enhanced (Gevensleben et al., 2012). Resting-state electroencephalogram (EEG) in the majority of children with ADHD is characterized by increased slow-wave activity and decreased fast-wave activity, primarily theta and beta activity respectively, and higher theta/beta and theta/alpha power ratios compared to controls (for review see Barry, Clarke, & Johnstone, 2003), often referred to as an hypo-aroused physiological state. Therefore most neurofeedback protocols focus on these frequency-bands (Monastra et al., 2005). A minority of children with ADHD has shown increased power of beta activity (Clarke et al., 2002), creating a subgroup with a hyper-aroused physiological state.

The placebo-controlled randomized trials published to date, have not found superior effects of EEG-neurofeedback compared to placebo-neurofeedback (Perreau-Linck et al., 2010; Lansbergen et al., 2011b; Arnold et al., 2012; van Dongen-Boomsma et al., 2013). In addition, a systematic review and meta-analysis of randomized controlled trials (RCTs) of non-pharmacological interventions in children with ADHD including EEG-neurofeedback studies, reported non-significant results for the blinded rating of symptoms (p = .07) (Sonuga-Barke et al., 2013).

Most studies have focused on behavioral outcome measures. However, it is worthwhile to examine whether EEG-neurofeedback is able to improve neurocognitive functioning in ADHD because the persistence of neurocognitive deficits is strongly associated with occupational problems and morbidity (Barkley & Murphy, 2010; Biederman et al., 2012).

The objectives of this paper were two-fold: (1) to systematically review the existing literature on the effects of two modalities of EEG-neurofeedback, namely frequency neurofeedback (F-NF) and Slow Cortical Potential neurofeedback (SCP-NF) on neurocognitive functioning and (2) to assess the effect of F-NF on neurocognitive functioning in a double-blind, placebo-controlled trial in children with ADHD.

Review on neurocognitive outcome measures after EEG-NF in children with ADHD

A literature research was carried out in PubMed for the period between January 1994 and May 2012 by combining the following MeSH terms; ('Attention Deficit Disorder with Hyperactivity'[MeSH]) AND ('Biofeedback, Psychology'[MeSH] OR 'Neurofeedback'[MeSH]). A final search was conducted to check for the most recent published trials (February 2013). The database search outlined above was supplemented by manual searches. The inclusion criteria that were applied to the publications retrieved were a) study was peer reviewed, b) diagnosis of ADHD was classified by the *Diagnostic and Statistical Manual of Mental Disorders* (3rd ed. *[DSM-III]*; American Psychiatric Association, 1980), *DSM-III-R* (American Psychiatric Association, 1987), *DSM-IV* (American Psychiatric Association, 1994), *DSM-IV-TR* (American Psychiatric Association, 2000), or the *ICD-10* (World Health Organization, 1992), c) age was in the range from 0-18 years old, d) the study was an RCT, e) F-NF and/or SCP-NF was used as treatment modality, f) neurocognitive data were reported in the publication. In total, 10 randomized controlled trials met these inclusion criteria (Linden, Habib, & Radojevic, 1996; Heinrich et al., 2004; Levesque, Beauregard, & Mensour, 2006; Leins et al., 2007; Holtmann et al., 2009; Perreau-Linck et al., 2010; Bakhshayesh et al., 2011; Steiner et al., 2011; Wangler et al., 2011; Arnold et al., 2013). See Table A1 *Overview studies*, in the appendix of this chapter.

The 10 selected EEG-neurofeedback studies were quite heterogeneous in their design and methodology. The studies included a range of different sample sizes and control conditions (e.g., passive control conditions vs. active control conditions). Investigators were blinded to treatment assignment in some studies while in others they were not. The neurofeedback-protocol as well as the duration, frequency, and number of sessions varied between studies. Significant differences between the studies were also noted in terms of the participants' characteristics (especially the use of medication), the statistical methods used, and the choice of neurocognitive tasks. The differences in neurocognitive tasks employed also rendered a meta-analysis impossible. However, areas in which the studies overlapped included the use of predominantly male participants in the same age range (mean around 10 years) as well as a common inclusion criterion that subjects must have a full-scale intelligence quotient (FSIQ) of more than 80 points.

Three of the 10 studies reported significant improvement on at least one neurocognitive variable for the NF condition superior to the control condition (Heinrich et al., 2004; Holtmann et al., 2009; Bakhshayesh et al., 2011). More specifically, treatment effects (i.e., time x group interaction) were seen for the variable representing impulsivity on the stop-signal task (Holtmann et al., 2009) and for all variables representing attention on the paper-and-pencil attention test (Bakhshayesh et al., 2011). However, in the paper-and-pencil attention test, the number of errors also increased significantly more in the F-NF condition than in the control condition, suggesting that improved speed came at the expense of accuracy. Note that speed-accuracy trade-off calculation was not reported. One study appeared to show a time x group interaction on the composite variable of the Kaufman-BRIEF Intelligence Test (K-BIT), a German intelligence scale. However, this was not explicitly reported (Linden et al., 1996). The study investigating the efficacy of SCP-NF showed a time x group effect for the variable representing impulsivity on a Continuous Performance Task (Heinrich et al., 2004).

Overall, these studies had many methodological limitations (including small sample sizes, increasing the chance for type II errors), and the majority failed to show positive neurocognitive effects of F-NF or SCP-NF. Taken together, these studies suggest that there is no systematic beneficial effect of these two types of NF on neurocognitive functioning.

Methods

Trial design

This study was designed as a triple-blind, placebo-controlled treatment trial, with stratified randomization for age (younger vs. older than 12 years old), electrophysiological state of arousal (hyper-arousal vs. hypo-arousal), and use of medication (with vs. without medication). After a pilot study (Lansbergen et al., 2011b), two adaptations were made: 1) In the F-NF condition, reward thresholds were changed from automatic into manual adjustment, resulting in the unblinding of the neurofeedback-therapist. Participants and raters remained blinded, creating a double-blind study. 2) Active learning strategies were implemented, so that children could apply the learned strategies into daily life.

Participants

Children (8-15 years old) were included if 1) they had been clinically diagnosed with ADHD according to the criteria of the *DSM-IV-TR* (American Psychiatric Association, 2000), 2) they had an FSIQ of at least 80, 3) their quantitative EEG (qEEG) deviated at least 1.5 standard deviations (SD) from normative data, 4) they did not use psychopharmaca or used a stable dose of ADHD medication, and 5) there was room for improvement, defined as a minimum score of 2 on a 4-point Likert scale (0-3) for at least 6 items of the ADHD Rating Scale IV (ADHD-RS) (Zhang et al., 2005). Children were excluded if they 1) were involved in psychotherapy, 2) used medication other than ADHD medication, 3) had a co-morbid disorder other than oppositional defiant disorder or any anxiety disorder, 4) had a neurological disorder and/or a cardiovascular disease, 5) participated in another clinical trial simultaneously, 6) had received neurofeedback in the past, or 7) used alcohol or drugs.

A doctor or psychologist screened potential children via a telephone interview with their parents in which ADHD symptoms and other psychiatric symptoms were checked. The Dutch version of the Social Communication Questionnaire (SCQ; Berument et al., 1999) was used to screen for autism spectrum disorders. The presence of other co-morbid disorders was assessed with the Diagnostic Interview Schedule for Children (Shaffer et al., 2000; Steenhuis et al., 2009). A positive screening-outcome was followed by a diagnostic procedure, including the ADHD-RS and a developmental and psychiatric interview with a child and adolescent psychiatrist. General functioning was measured by the Children's Global Assessment Scale (CGAS; Shaffer et al., 1983) and the severity of ADHD was assessed with the Clinical Global Impressions-Severity scale (CGI-S; Guy, 1976). If an intelligence test had not taken place over the past 1.5 years, two subtests of the Wechsler Intelligence Scale for Children (WISC-III) were administered (i.e., Vocabulary and Block Design) to estimate intelligence (Wechsler, 1991). Finally, 20 minutes (min) of clean raw EEG in an eyes-open and eyes-closed condition was acquired to determine deviation from the NeuroGuide database (Thatcher et al., 2003).

Recruitment started in August 2008 and ended in May 2012. Children were recruited from referrals to Karakter Child and Adolescent Psychiatry University Centre in Nijmegen, and from responders to advertisements in the journal of the Dutch Parents Association for Children with Developmental Disorders. The study was approved

by the Dutch Central Medical Ethics Committee (www.ccmo.nl) and conducted in accordance with the declaration of Helsinki. All parents and children older than 12 years gave their written informed consent before participation; children younger than 12 years gave oral assent. Travel costs were partially reimbursed. All children received a 10-euro gift certificate and a small present after collecting 30 stickers, given after each session.

The study was registered in the Clinical trial register under 'Project ADHD and EEG-Neurofeedback THERapy'; www.clinicaltrials.gov; NCT00723684.

Interventions

The *Neurofeedback Instituut Nederland B.V.* provided both the F-NF and the placebo neurofeedback (PL-NF) training. Individualized F-NF protocols based on visual inspection of the raw EEG and qEEG were used for F-NF training.

The F-NF training was intended to normalize power within individually determined frequency-bands and electrode sites by receiving feedback on their real-time EEG-signal. In this study, personalized protocols were used to address different EEG abnormalities, i.e., hypo-arousal vs. hyper-arousal, in children with ADHD, consisting of a protocol focusing on the EEG abnormality in that child. The individually applied protocols can be found in the *EEG protocols* (Table A2 of the appendix of this chapter).

Children watched a film for 20 min in an 'active focusing state' with eyes open. They were instructed to attempt to self-regulate their brain activity. Positive feedback was provided by brightening the computer screen and presentation of auditory tones. Most children in the F-NF group were trained to increase the presence of the sensory motor rhythm (SMR) or low-beta activity while simultaneously suppressing the presence of theta activity, meaning that when the production of SMR remained above threshold, and/or the theta/beta remained below threshold, positive feedback was given. Reward threshold levels were manually adjusted to 80% for each training target (i.e., frequency- band and/or location). Therefore, the actual percentage reinforcement depended on the amount of co-occurrence of desirable activity towards training targets (e.g., theta power going downwards at P3 while simultaneously going downwards at P4). Reinforcement was 80% when all training

targets were achieved simultaneously only. When assuming no correlation in activity between the different training targets, the reinforcement was 0.8 to the power of the number of training targets (e.g., training theta power downwards and beta power upwards resulted in a rewarding percentage of 64%). In practice, the reinforcement lay between 0.8 and 0.8 to the power of the number of training targets. Thresholds were manually adjusted according to the expertise of the neurofeedback-therapist. No specific guideline or protocol was followed. This method was in line with the objective of this study to investigate the efficacy of neurofeedback as delivered in 'care as usual', in which decisions about adjustments of the threshold are determined by the involved clinical neurofeedback-therapist. All of the neurofeedback-therapists were BCIA certified (Biofeedback Certification International Alliance, 10200 W 44th Ave, Suite 310, Wheat Ridge CO 80033-2840). An identical procedure was provided in the PL-NF group, except that children in the PL-NF group received feedback on a simulated EEG signal, consisting of a random signal similar to real EEG, in accordance with the procedure of an earlier study (Logemann et al., 2010). BrainMaster Atlantis hardware and software provided both training modalities (BrainMaster Technologies; Bedford, Ohio). Feedback on real EEG and simulated EEG signals seemed similar in experience in an earlier study and in our pilot study (Logemann et al., 2010; Lansbergen et al., 2011b). The behavioral effects of this study were described in **Chapter 3**.

Neurocognitive outcomes

All children included in the study underwent a neurocognitive assessment of 90 min before and after treatment. Two versions of the neurocognitive battery controlled for a possible task-order effect. If available, different versions of the tasks were administered before and after the treatment to control for a potential learning effect. Complete task descriptions can be found in the *Neurocognitive task descriptions* of the appendix. Below, the neurocognitive tasks are briefly described.

Sustained Attention Dots task (SA-DOTS)

The Continuous Performance Task from the computerized neurocognitive test-battery of the Amsterdamse Neuropsychologische Taken (ANT; de Sonneville et al., 1990; de Sonneville, 1999) was used to measure sustained attention. Variables of interest were the number of correct responses, the mean reaction time (RT) in milliseconds (ms) on correct responses and its standard deviation, and the number

of premature responses (RT < 150 ms). Note there was a trade-off to be made between RT and accuracy. Therefore, the expected (negative) relationship between RT and number of correct trials was addressed by performing similar analyses while controlling for each other.

Visuospatial Sequencing (VSS)

To measure visuospatial memory, the VSS subtest from the ANT (de Sonneville, 1999) was used. The number of correct trials and the number of targets identified in the correct order were determined and used for analyses.

Digit Span from the Wechsler Intelligence Scale for Children-III (DS-WISC-III)

To measure verbal working memory, the digit span (forward and backward) from the WISC-III (Wechsler, 1991; de Kort et al., 2002) was used. The total number of correctly recalled forward digit-sequences and backward digit-sequences compared to an age-norm was the variable of interest.

The Rey Auditory-Verbal Learning Test (RAVLT)

Verbal working memory and long term verbal memory was assessed using the Dutch adaptation of the RAVLT. In the Dutch version Rey's procedure (Rey, 1964) is applied without an interference trial (van den Burg & Kingma, 1999). In this form, the AVLT was administered in the present study. The total number of immediately recalled words over all five presentations and the amount of words recalled 20 min after the last presentation were chosen as the variables of interest.

Instrumental Learning task

Instrumental learning tasks are widely used instruments that have their origin in the instrumental/operant learning principle (Thorndike, 1898). A version of this task appropriate for children was created derived from two example instrumental learning paradigms (O'Doherty et al., 2004; Pessiglione et al., 2006). The variables of interest were the total number of choices of high versus low probability actions in reward trials and the trial at which the learning criterion was reached. The learning criterion was defined as 8 consecutive high probability actions.

Time Production task

To measure precision of time perception, a time production task was constructed based on the task description of van Meel et al. (2005). The mean absolute

discrepancy and its standard deviation between stimulus length and response length were measured.

Time Reproduction task

To measure precision of time reproduction, a task was constructed based on the task description of Rommelse et al (2007). The mean absolute discrepancy and its standard deviation between stimulus length and response length were measured.

Sample size

Sample size was calculated for the primary outcome and was based on the following considerations. Double-blind, placebo-controlled trials have shown an effect size (ES) of 0.6 or more for the first-line treatment of ADHD with medication (Michelson et al., 2002; Faraone & Buitelaar, 2010). Pilot open-label studies with EEG-neurofeedback also report an ES around 0.6 (Fuchs et al., 2003). With an alpha error of .05, a sample of 60 children in the EEG-neurofeedback arm and 60 in the placebo-neurofeedback group and a power of 80% would enable treatment effects to be detected with an ES of 0.5.

Randomization

Participating children were stratified and subsequently randomly assigned (1:1 assignment using random block sizes of two), double-blindly, to either F-NF or PL-NF. The principal investigator who was not involved in data collection performed this. Randomization by means of minimization was applied, including EEG profile, age, and medication use as factors (Han, Enas, & McEntegart, 2009). The treatment group that most strongly would minimize the imbalance was chosen to allocate the participant.

Blinding

All people involved in the study were blinded to treatment assignment, except the neurofeedback-therapist and the principal investigator, who were not involved in data collection, data entry, and data analysis.

Statistical methods

As first step, we analyzed all neurocognitive variables at group level. Variables of the Instrumental Learning task, Time Reproduction task, and the Time Production task were created using MATLAB R2009a (The Math-Works, Inc., Natrick, MA). All statistical analyses were conducted employing the IBM SPSS Statistics, version 20.0 (Armonk, New York; IBM Corp.). The significance level was set at $p = .05$. Imputation of missing data was used to obtain the most accurate data set (Donders et al., 2006).

To optimize control for the variance at baseline, baseline was used as a covariate in analyses of the covariance (ANCOVA). For each neurocognitive parameter the endpoint measurement was the dependent variable while the baseline measurement was a covariate, and group (F-NF vs. PL-NF) was the fixed factor.

To reduce within-group error variance and to eliminate confounding, additional ANCOVAs were performed (Field, 2009). For all main analyses, we also conducted ANCOVAs with age, gender, FSIQ, medication use, and electrophysiological arousal as covariates to control for their possible influence.

To confirm the reliable use of ANCOVA, all required assumptions were tested per variable, except the assumption for independence of the sample, which was not expected to be present in this experimental design and the independence of the covariate and treatment effect, which was covered, by randomization and stratification. B-weights, the unstandardized regression coefficients, represent the relationship between the groups and the outcome variable included in the analysis. In this study, a positive value indicates an effect for the F-NF group, a negative value an effect for the PL-NF group. The significance on the t-tests tells whether this relationship is significant.

The next step was to examine whether participants might show significant and reliable individual changes on neurocognitive variables that might be overlooked at group level. The Reliable Change Index (RCI) was used to address this issue. The RCI-method, described by Jacobson & Truax (1991) was subsequently applied to a placebo-controlled medication study in children with ADHD (Buitelaar et al., 1995). This method was also used by another NF study (Perreau-Linck et al., 2010). The RCI was calculated for each individual, *i*, using the following formula:

$$RCI = \frac{D_i - P_i}{SE}$$

In which D_i is the observed change between pre- and post- measurement, P_i the mean change score of the placebo group, and SE the corresponding standard error. If a child exceeded the critical value of (-)1.96 (equaling our significance value set at $p = .05$), it was said to reliably change on this measure.

Results

The demographic and clinical characteristics are described in Table 1. In sum, 41 children (mean age 10.6 ± 2.3, 83.0 % boys, and estimated FSIQ of 105.7 ± 16.7) were included. Of these, 22 children were assigned to the F-NF group (8 of the pilot-study, 14 post pilot-study) and 19 children to the PL-NF group (no differences made after pilot). Analyses with respect to the neurocognitive results performed on the sample without the pilot-study sample (n = 33) and the total sample (n = 41), did not yield different results, and therefore data of the total sample is being presented. Further, we tested for blinding of the participants. This test revealed that guessing treatment assignment was not better than at chance level ($p = .224$ for children, $p = .643$ for parents). For a complete overview of the clinically examination procedure and the administered NF, see *EEG protocols* and *CONSORT flow diagram* in *Figure A1* and Table A2, both in the appendix of this chapter.

Table 1. Demographic characteristics

Characteristics	Frequency neurofeedback (N = 22)	Placebo-neurofeedback (N = 19)	Analysis t, χ^2 p-value
Age, M (SD), y	10.5 (2.2)	10.7 (2.3)	$p = .734$
Gender (%)			$p = 1.000$
male	86.4	78.9	
female	13.6	21.1	
Race (%)			$p = 1.000$
Caucasian	91	95	
Black	9	5	
Full scale IQ, m (SD)	108.8 (19.4)	102.1 (12.2)	$p = .205$
Medication for ADHD (%)			$p = .726$
psychostimulants	50	73.7	
atomoxetine	4.5	0	
no medication	45.5	26.3	

Table 1. Continued

Characteristics	Frequency neurofeedback (N = 22)	Placebo-neurofeedback (N = 19)	Analysis *t*, χ^2 *p*-value
EEG arousal (%)			*p* =.513
hypo-aroused	86.4	73.7	
hyper-aroused	13.6	26.3	
ADHD subtype (%)			*p* =.543
combined	77.3	68.4	
inattentive	18.2	26.3	
hyperactive/impulsive	4.5	5.3	
Co-morbidity (%)			
oppositional defiant disorder	22.7	5.3	*p* = .191
anxiety disorders	13.6	10.5	*p* = 1.000
dyslexia	9	15.8	*p* = .649

Abbreviations: N: number; *t*: independent sample t-test; χ^2: chi-square test; *p*: probability; M: mean; SD: standard deviation; y: years; IQ: Intelligent Quotient; EEG: electroencephalographic.

Neurocognitive characteristics

All variables were distributed normally within groups, unless specifically stated and dealt with accordingly (e.g., by removing outliers, defined as 25% of the size of the largest leaf entry in the clustering feature tree, based on the default definition used by SPSS 20.0). All assumptions confirmed permission for using ANCOVA as statistical test method. However, for some variables removing outliers was needed to meet these assumptions. A maximum of 4.9% was removed in favor of creating a normal distribution. Imputation of missing data was used for the SA-DOTS, the VSS, the Instrumental Learning task, and the Time Reproduction task with an average of 4.9% and a maximal imputation of 14.6%. Table 2, gives an overview of baseline values and shows that there was no difference between groups at baseline.

Neurocognitive outcomes

All main outcomes are depicted in Table 2 and *Figure 1*.

Sustained Attention Dots task (SA-DOTS)

Two outliers were detected in the F-NF group and three in the PL-NF group. No treatment effect was found on any of the variables (correct: $t(33) = -0.090$, $p = .928$; RT: $t(33) = 0.868$, $p = .385$; SD of RT: $t(33) = 0.109$, $p = .913$). When additionally controlling for the number of correct trials, RT still did not reveal a treatment effect ($t(32) = 0.864$, $p = .387$). Likewise, the number of correct trials did not reveal a

treatment effect after additionally controlling for RT ($t(32) = -0.075, p = .940$). Making more than eight premature responses was defined as an outlier. After treatment no difference in premature responses between groups was found (Fisher's Exact Test: $p = 1.000$).

Visuospatial Sequencing (VSS)

Two outliers were detected in the F-NF group and excluded from the dataset. The number of correct trials after controlling for baseline score did not show a treatment effect ($t(36) = -0.672$, $p = .502$), neither did the number of targets identified in correct order ($t(36) = -0.810$, $p = .418$).

Digit Span from the Wechsler Intelligence Scale for Children-III (DS-WISC-III)

No significant treatment effect was found on the norm-score of forward and backward DS after controlling for the baseline-score ($t(38) = 0.586$, $p = .561$).

The Rey Auditory-Verbal Learning Test (RAVLT)

No significant treatment effect was found on direct- and delayed recall after controlling for the baseline-score (direct: $t(38) = 0.591$, $p = .558$; delayed: $t(38) = -0.290$, $p = .773$).

Instrumental Learning task

Two outliers were detected in the PL-NF group when exploring the data and were excluded from the dataset. No treatment effect was observed on the number of high probability actions ($t(36) = 1.003$, $p = .316$) or on the moment at which the learning criterion of 8 consecutive high probability actions was reached ($t(36) = -0.028$, $p = .978$).

Time Production task

Two outliers were detected in the F-NF group and excluded from the dataset. No significant treatment effect was found on the mean absolute deviation (MAD; in ms) from 1 second after controlling for baseline-score ($t(36) = 0.599$, $p = .553$). A trend towards more variance in response length (standard deviation of MAD) in the F-NF than PL-NF group was observed ($t(36) = 1.833$, $p = .075$).

Table 2. Baseline and endpoint scores on all neurocognitive parameters. Also depicted are the change scores between baseline and endpoint and the mean individual interaction effect size

Neurocognitive parameter (M and SD)	Baseline[a]		Endpoint		Change score		Effect size[b] Cohen's *d*
	F-NF (N ≤ 22)	PL-NF (N ≤ 19)	F-NF (N ≤ 22)	PL-NF (N ≤ 19)	F-NF (N ≤ 22)	PL-NF (N ≤ 19)	
Sustained Attention Dots							
correct trials	551.9 (31.5)	556.6 (29.6)	549.2 (29.7)	555.5 (32.2)	-0.9 (14.9) ↓	-0.8 (25.1) ↓	-0.01
response time correct trials	3417.2 (873.6)	3434.9 (824.5)	3146.7 (1058.1)	2981.5 (653.5)	-354.5 (571.9)	-511.7 (342.4)	0.34
SD response time correct trials	1533.8 (736.8)	1649.6 (674.5)	1464.9 (891.8)	1504.3 (777.2)	-155.5 (551.9)	-212.5 (336.8)	0.13
Visuospatial Sequencing							
correct trials	19.6 (2.5)	18.3 (2.9)	19.1 (3.8)	19.4 (3.3)	0.0 (3.7)	1.1 (3.0)	-0.34
identified in correct order	90.9 (9.7)	86.7 (10.8)	87.6 (16.0)	90.3 (12.0)	-1.5 (15.3) ↓	3.8 (11.2)	-0.42
Digit Span-WISC-III							
z-score forward and backward	10.6 (3.2)	10.0 (2.7)	11.5 (3.4)	11.5 (2.4)	0.9 (2.8)	1.5 (2.2)	-0.24
RAVLT							
direct recall	46.6 (8.4)	44.2 (6.7)	45.5 (9.0)	45.1 (7.0)	-1.1 (7.5) ↓	0.9 (6.0)	-0.30
delayed recall	9.7 (2.6)	9.6 (2.5)	9.7 (2.5)	9.8 (2.5)	0.0 (2.5)	0.2 (2.2)	0.15
Instrumental Learning task							
high probability action	44.8 (3.9)	44.9 (4.1)	42.5 (7.3)	40.2 (7.2)	-2.3 (8.2) ↓	4.8 (7.9)	-0.90
reach learning criterion	17.3 (2.7)	16.8 (2.0)	17.9 (4.6)	18.0 (4.5)	0.6 (5.8) ↓	1.2 (4.4) ↓	-0.12
Time Production task							
MAD from 1 sec (ms)	205.5 (80.4)	224.9 (74.0)	228.2 (113.7)	230.4 (83.8)	22.7 (83.8) ↓	5.5 (65.0) ↓	0.23
SD from MAD (ms)	182.5 (76.2)	208.2 (84.4)	338.1 (473.0)	209.7 (102.8)	155.5 (429.5) ↓	1.5 (97.2) ↓	0.50
Time Reproduction task							
MAD from trial (ms)	2043.2 (1254.0)	2694.4 (1740.2)	2672.4 (1604.7)	2388.5 (1556.2)	473.9 (949.3) ↓	310.3 (1258.5) ↓	0.15
SD from MAD (ms)	2178.1 (1584.8)	2947.5 (1644.2)	3089.6 (1597.1)	2317.6 (1281.6)	734.1 (1453.1) ↓	619.6 (1412.3) ↓	0.08*

*$p < .05$.

Note: Data were used without using imputed data or outliers. [a] Independent sample t-tests between groups for which $p > 0.20$. [b] Time x group interactions of repeated measures ANOVAs for which $p > .10$.

Abbreviations: M: mean; SD: standard deviation; F-NF: frequency neurofeedback; N: number; PL-NF: placebo-neurofeedback; Cohen *d*: the difference between groups (PL-NF subtracted from F-NF) for the change scores between endpoint and baseline divided by the pooled standard deviation of the change scores taking into account the sample size; ↓: direction of the change score in opposite direction than direction hypothesized to be improvement; Digit Span-WISC-III: Digit Span from the Wechsler Intelligence Scale for Children-III; RAVLT: Rey Auditory Verbal Learning Test; MAD: mean absolute deviation.

Time Reproduction task

No significant treatment effect was found on the MAD from the trial ($t(38) = 1.771$, $p = .077$). A significant treatment effect, the F-NF fluctuating more in response length than the PL-NF, was observed on the SD of MAD ($t(38) = 2.674$, $p = .008$).

Covariates analyses

To control for the influence of age, gender, FSIQ, medication, and electrophysiological arousal, these variables were added as covariates to the main ANCOVA with the neurocognitive parameter as dependent variable, and group as fixed variable. These analyses did not reveal any significant treatment effects and also abolished the previous ANCOVA-results that suggested a potential treatment effect.

Reliable Change Index

Similar to results of Perreau-Linck and colleagues (2010), each participant improved on at least one measure, however, each participant also deteriorated on at least one measure. *Figure 2* displays the percentage children that showed improvement and deterioration per group for each variable. These results did not yield a different conclusion than group analyses did; i.e., F-NF was not superior to PL-NF in improvement on the neurocognitive measures. When focusing on the few children that showed a significant behavioral improvement (i.e., a clinical response), see **Chapter 3**, each of these children showed improvement on some neurocognitive measures but deterioration on others.

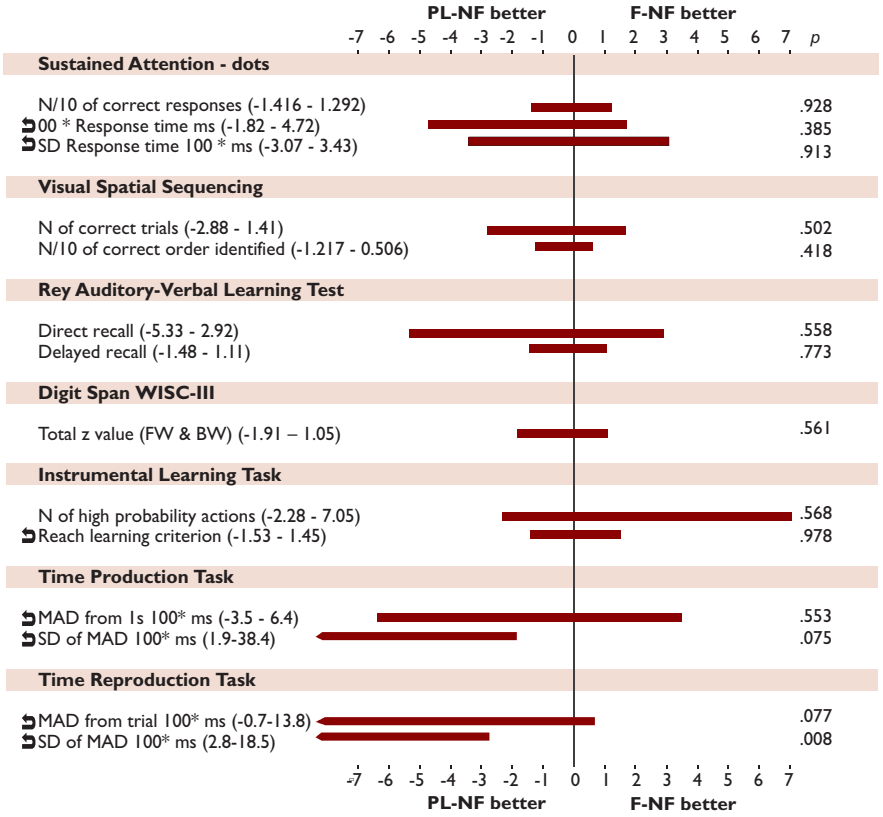


Figure 1. 95% confidence intervals for each neurocognitive parameter

Based on B-weights, this figure shows that despite a relatively small sample size and thus limited statistical power, there is no reason to reject the null-hypothesis. A positive value indicates an effect for the EEG-neurofeedback group; a negative value indicates an effect for the placebo-neurofeedback group.

Note: Values of which lowering is hypothesized to be an improvement, are indicated with a preceding arrow (↩) and scales are inverted.

Abbreviations: PL-NF: placebo-neurofeedback group; F-NF: frequency neurofeedback group; *p*-value: probability-value; N: number; ms: milliseconds; SD: standard deviation; Digit Span-WISC-III: Digit Span from the Wechsler Intelligence Scale for Children-III; FW: forward; BW: backward; MAD: mean absolute deviation; s: seconds.

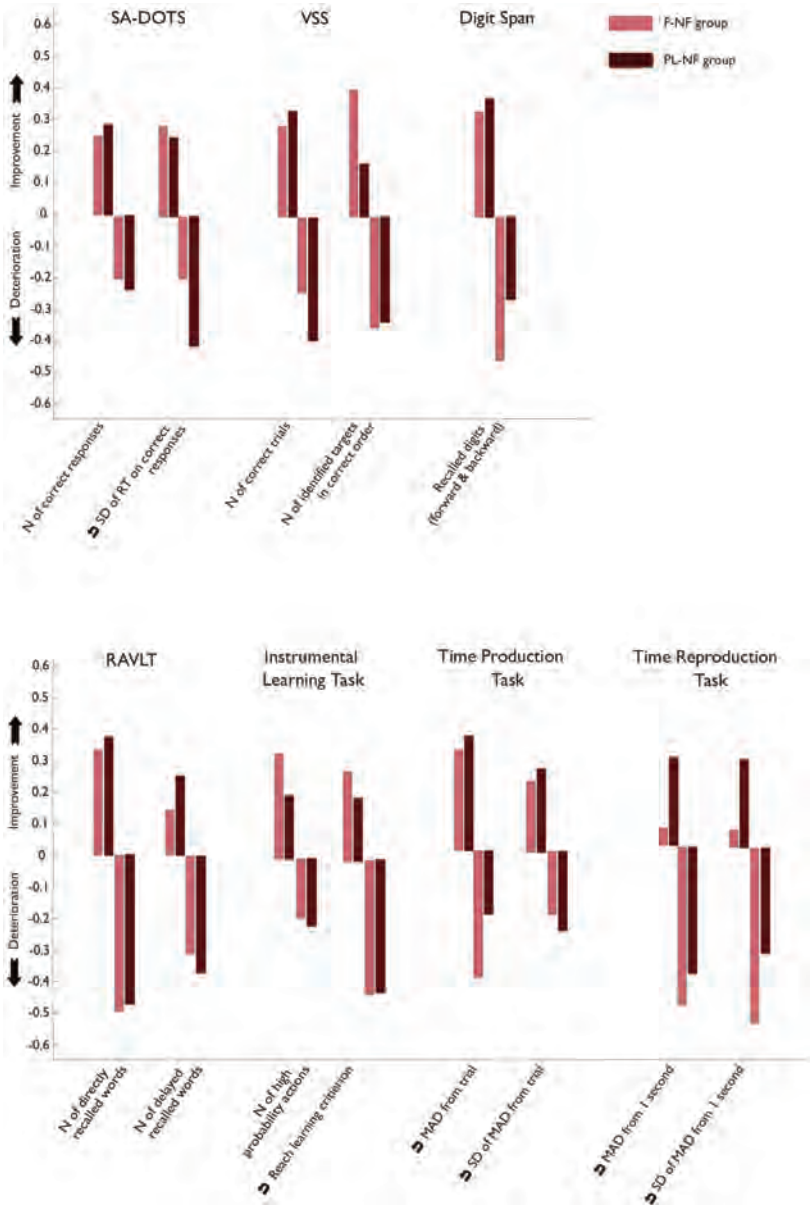


Figure 2. Proportion of children that shows improvement or deterioration on the Reliable Change Index per group for each variable

Note: The preceding arrow (↩) indicates an inverted scale; values of which lowering is hypothesized to be an improvement.

Abbreviations: SA-DOTS: Sustained Attention Dots; VSS: Visuospatial Sequencing; Digit Span-WISC-III: Digit Span from the Wechsler Intelligence Scale for Children-III; F-NF: frequency neurofeedback; PL-NF: placebo-neurofeedback; N: number; SD: standard deviation; RT: reaction time; RAVLT: Rey Auditory Verbal Learning Test; MAD: mean absolute deviation.

Post-hoc analyses of the F-NF training

EEG-data during the sessions were available for 10 children (14 children were part of the pilot group in which EEG recordings were not saved and for 4 additional children, data were missing). Mean power was calculated per trained frequency-band and electrode for the first, 10th, 20th, and last session. Seven children showed a change in power towards one of the training targets. However, the variability between sessions was great and no children showed such a desired change in more than one frequency-band. Moreover, all children additionally showed a change in power away from a training target. Clinical responders showed an EEG change in the desired as well as non-desired direction.

Discussion

This study evaluated whether or not F-NF had beneficial effects on neurocognitive functioning in children with ADHD, based on the results of our placebo-controlled double-blind design, and on a review of the existing literature.

No significant improvement of neurocognitive functioning after F-NF compared to PL-NF was found, which is in line with previous analyses of behavioral effects on the same dataset (see **Chapter 3**). Participants who showed positive behavioral responses to F-NF did not show any sign of neurocognitive improvement. In addition, RCIs assessing individual changes in neurocognitive measures for each participant yielded essentially the same results. Furthermore, the only significant interaction effect found was in favor of the PL-NF.

The systematic review suggests that neurocognitive improvements occur over time, but when compared with the control conditions, only two out of the nine RCTs reported a treatment effect of F-NF on some neurocognitive variables (i.e., impulsivity and attention). The findings of these two RCTs are likely based on chance since the family-wise error rate is large when conducting such a high number of statistical tests. Also, the few papers that report neurocognitive improvements had significant methodological limitations.

The most likely explanation why we did not find improvement of neurocognitive functioning after F-NF is that F-NF is not an effective treatment in ADHD. This conclusion is in line with three recently published placebo-controlled F-NF studies reporting no superior effect on the core-behavior symptoms of ADHD (Perreau-Linck et al., 2010; Lansbergen et al., 2011b; Arnold et al., 2013; **Chapter 3**). Yet another explanation is that neurocognitive improvement takes longer to manifest and may only be detectable at later time periods after end of the study. Furthermore, the results are based on a selected battery of neurocognitive tests, reflecting neurocognitive functions hypothesized to be impaired in ADHD (Nigg, 2005). The battery focussed more on attentional processes, because these have been shown to be most sensitive to EEG-NF on behavioral level (Arns et al., 2009). However, not all hypothesized impaired neurocognitive functions were (fully) represented by the chosen test-battery, as is the case for conflict resolution and inhibition. The current study was conducted with care, especially with respect to study design and implementation of a comprehensive neurocognitive test-battery. Due to the requirement of a deviant pre-treatment EEG, this study enabled the child to train specific EEG deviations, in line with the hypothesis that EEG-NF improves or even normalizes deviant pre-treatment brain activity. This requirement did not lead to generalizability problems, because 95% of the participating children did have a deviant pre-treatment EEG.

Nevertheless, this study has some limitations. First, children with all subtypes of ADHD and with an FSIQ of at least 80 points were included in this study. Thus, clear findings of improvements in subgroups of ADHD or children with a significant lower IQ cannot be made. Second, the current cohort is smaller in size than planned, due to recruitment difficulties. Especially the F-NF pilot group, which could have shown improvement driven by implemented learning strategies, was small (N = 14). However, all 95%-CIs of the B-weights, the unstandardized regression coefficients (*Figure 1*) are centered around zero, which suggests that the marginal effects that were found for three parameters were possibly based on chance. Type II errors due to a lack of power are therefore less likely than if the 95%-CIs had not been centered around zero. The RCI analyses also suggest that power was not the most likely explanation of the failure to find an effect. Third, the neurofeedback-therapist was not blinded, allowing for the possibility of a different attitude or bias towards the child, depending on group assignment. Fourth, to arrive at a normal distribution, up to 4.9% of the data was removed and to deal with missing data, imputation was

used for an average of 4.9%, up to 14.6% of the data. Although these procedures were necessary to perform analyses in the most valid way, these procedures are still regarded as limitations of the study. It should also be noted that the current findings are based on a Caucasian sample and thus should not be presumed to be applicable to other races. Finally, this study aimed to investigate neurofeedback training delivered in 'care as usual'. Applying 80% positive feedback per condition leaded to a relatively low amount of reward in the more complex protocols. This decision was made in congruency with 'care as usual', but adds a limitation to this study-design. Furthermore, EEG-data from children in the F-NF group (after the two protocol adaptations) recorded during the sessions, showed that not all desired training directions were met. Significant improvement on group level can only solidly be interpreted if all training conditions hypothesized to improve ADHD (on either behavioral or neurocognitive level) are actually improved in the desired direction. In 'care as usual', decisions about adjustments of the threshold were determined by the involved clinical neurofeedback-therapist. Future research should focus on different ways to deliver neurofeedback. In addition, the influence of F-NF on neurocognitive domains not covered by the current study therapy should be investigated.

This study was unable to establish positive treatment effects on neurocognitive functioning after F-NF compared to PL-NF. This finding is in line with a systematic review of the current literature, but maybe influenced by the existing study limitations.

Appendix

EEG protocols

Table A2. Characteristics of the administered EEG-neurofeedback for the EEG-neurofeedback group

Participant	Electrode position	Low frequencies (Hz) train downwards	Beta, low range (Hz) train upwards	Beta, high range (Hz) train downwards
1	F3, F4	4-7	12-15	20-30
2	F3, F4	4-7	12-15	20-30
3	C3, C4	4-7	12-15	
4	P3, C4	4-6	12-15	
5	P3, P4	4-7	12-15	
6	Fz	4-7	12-15	
7	C3, C4	4-7	12-15	
8	C3, C4		12-15	15-20 + 20-25
9	P3, P4	4-5	12-15	24-27
10	F3, F4	4-7	12-14	20-30
11	F3, F4		11-13	18-23 +24-28
12	CZ	4-7	15-20	
13	CZ	4-7	12-16	
14	P3, P4		11-13 +12-15	20-25
15	Fz	3-5	12-15	15-18
16	F3, F4	3-5	12-15	
17	C3, C4	5-7	12-15	
18	CZ	3-4	15-18	
19	F3, F4			15-18 +18-20
20	P3, P4	3-6	12-15	
21	CZ	3-7	12-15	
22	CZ	4-7	15-18	

Note: Electrode positions are according to the international 10-20 system. The trained frequencies deviated 1.5 SD or more from the normative NeuroGuide database and were trained in the opposite direction.

Abbreviations: SD: standard deviation; EEG-neurofeedback: electroencephalographic neurofeedback; Hz: Hertz.

Table A1. Overview studies.

Study	Age (years)[1] (M, SD)	N (total) *N (F-NF)* *N (controls)*	Duration Frequency N sessions	Blinding P R NFT	NC- tests	Results[2]	Rresults[2] Cohen's *d*
Linden et al. 1996	5-15	18 *9 (F-NF)* *9 (WL)*	45 minutes 2/week 40 sessions	P: no R: yes NFT: NAP	K-BIT	***K-BIT****	1.26
Heinrich et al. 2004	10.8 (1.8)	22 *13 (SCP-NF)* *9 (WL)*	50 minutes 5/week 25 sessions	P: no R: no NFT: no	CPT	***CPT Impulsivity errors****	-0.39
Lévesque et al. 2006	10.2 (0.9)	20 *15 (F-NF)* *5 (no F-NF)*	60 minutes 3/week 40 sessions	No blinding	IVA-CPT Digit Span c- Stroop	IVA-CPT *** Digit Span* c- Stroop*	0.34 0.17 0.94-1.18
Leins et al. 2007	9.2 (1.5)	38 *19 (F-NF)* *19 (SCP-NF)*	60 minutes 5/week[3] 3x10 sessions	P: yes R: NA NFT: no	TAP-7 HAWIK-II	TAP-7 for theta/beta*[4] HAWIK-II for theta/beta**** TAP-7 for SCP***-***** HAWIK-II for SCP***	0.66, -[4] 0.82 0.92-1.09, 0.77 0.54
Holtmann et al. 2009	10.3 (1.2)	34 *20 (F-NF)* *14 (CAST)*	30 minutes 2/week 20 sessions	P: no R: NA NFT: no	Stop signal-t	***Stop signal-t impulsivity********	-1.03
Perreau-Linck et al. 2010	10.4 (1.7)	9 *5 (F-NF)* *4 (PL)*	60 minutes 2/day[5] 40 sessions	P: yes R: no NFT: yes	CPT Digit Span Spatial span VF/CWI-t Key search Zoo map Six part test Beels/Mesula's-ct Child CAT TEA-ch D2	All participants showed significant change in the desired direction on at least one measure with equivalent change occurring in both groups.	-

Wangler et al. 2011	9.6 (1.2)	94 *59 (F-NF/SCP-NF)* *35 (AST)*	50 minutes 2/day[6] 36 sessions	P: no R: yes NFT: no	ANT CPT[7]	ANT** - ****	-0.345-0.171
Bakhshayesh et al. 2011	9.3 (1.9)	35 *18 (F-NF)* *17 (EMG-F)*	30 minutes 2-3/week 30 sessions	P: no R: NA NFT: no	p-p attention-t CPT	***p-p attention-t*** *-**** [8] CPT**	0.68-0.99 -0.70
Steiner et al. 2011	12.4 (0.9)	36 *10 (F-NF)* *11 (SCF-AT)* *15 (WL)*	30 minutes 2/week 32 sessions	No blinding	IVA-CPT	No significant effects at all	-

Note: [1] If mean and standard deviation were not available, the inclusion criterion was given. [2] Results are represented by Cohen's *d* interaction when there were significant time effects. Time effects are depicted in standard black and time x group effects in italic and bold in favor of the frequency neurofeedback group. If there are no time effects and/or time x group effects in favor of the frequency neurofeedback group, these are not mentioned. [3] 3 phases of 10 sessions in two weeks, breaks of 4-6 weeks in between, transfer trials between phases. [4] Since this study contained active treatment groups only, time effect rather than treatment effects are given. Time effects consisted of either baseline-endpoint or baseline-follow-up measurements. Analyses were performed for 'below and above average achievers' and are reported as such respectively, separated by a comma. [5] spread over 7-9 weeks. [6] 2-3 times a week with a break of 2-3 weeks between the two blocks. [7] Due to adaptation of the CPT during the study, the authors decided not to publish the results (personal communication with one of the authors). [8] On the paper-and-pencil attention test, there are time-effects for the variables speed and total concentration score, but also for the variable error. So the effects on variable error are in the opposite direction. Time x group effects are seen for these variables too, and also for the variable reaction time. For the CPT there was a time effect for commissions only.

*p = < .05, **p = <.01, ***p = < .005, ****p = ≤ .001. When different p-values are within one test, the minimum and maximum p-values are presented. When there is also a time x group interaction, only this p-value is reported.

Abbreviations: M: mean; SD: standard deviation; N: number; F-NF: frequency neurofeedback; P: participant; R: rater; NFT: neurofeedback-therapist; NC-tests: neurocognitive tests; Cohen's *d*: effect size of interaction; et al..: et alii, meaning 'and others'; WL: waiting list; NAP: not applicable; K-BIT: Kaufman-BRIEF Intelligence Test; SCP-NF: Slow Cortical Potential-neurofeedback; CPT: continuous performance task; IVA-CPT: Integrated Visual and Auditory Continuous Performance Task; c-Stroop: counting Stroop; NA: not available; TAP-7: Testbatterie zur Aufmerksamkeits-prufung; HAWIK-II: Hamburger-Wechsler-Intelligentenztest fur Kinder; CAST: Computerized Attention Skills Training; -t: test; PL: placebo; VF/CWI-t: Verbal Fluency Color Word Interference test; Beels/Mesula's-ct: Beels and Mesula's cancellation task; Child CAT: Children's Apperception Test; TEA-ch: Test of Everyd; d2: d2 Test of Attention; AST: Attention Skills Training; ANT: Attentional Network Test; EMG-F: electromyograph-feedback; p-p attention-t: paper-and-pencil attention test; SCF-AT: Standard Computer Format-Attention Training; tx: tests; W-abbr.-IQ: Wechsler Abbreviated Scale of Intelligence; BRC-tx: 7 Brain Resource Center computer-based normed neuropsychological tests.

CONSORT flow diagram

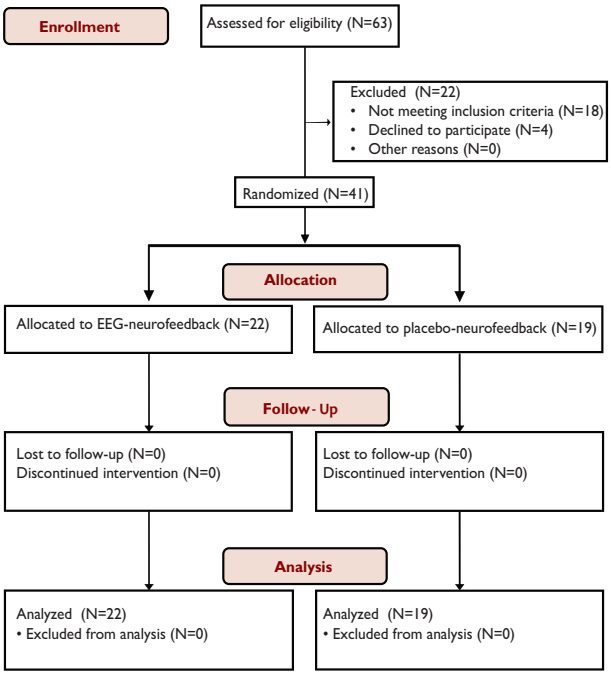


Figure A1. CONSORT flow diagram of study participants

Abbreviations: CONSORT: Consolidated Standards of Reporting Trials, N: number; EEG: electroencephalogram

Neurocognitive task descriptions

Sustained Attention Dots task

Dot patterns of random asymmetric 10 x 10 centimeter configurations were randomly presented. Children covered the buttons of a mouse with both hands using their index fingers and had to response 'yes' with their dominant hand if a four-dots pattern was presented, and 'no' with their non-dominant hand if a three- or five-dots pattern was presented. In case of an opposite response an audible error-signal was presented. The interval between a response and the next stimulus was fixed at 250 milliseconds (ms). Reaction times were allowed to vary between 150 and 1000 ms. Responses outside these bounds were labeled as non-valid trials and therefore automatically replaced by a new trial. After 12 practice trials, a total of 600 valid trials were presented in 20 – 30 minutes (min).

Visuospatial Sequencing

In a 3 x 3 matrix of nine circles, several circles were pointed at with a computer-driven hand. Children had to point at the same circles in correct order with a self-driven hand without having any time constraints. Difficulty level increased after every correct trial by an increase in number of circles or by an increase in complication of the spatial pattern, hence the distance between circles pointed at. One practice trial and a fixed amount of 24 experimental trials were presented in 5 – 10 min.

Digit Span from the Wechsler Intelligence Scale for Children-III

In the first block, sequences of digits were verbally presented, which the child had to repeat in forward order in the first block and in backward order in the second block. The maximum sequence-length depended on the number of correctly repeated sequences. For each block, 2 trials of each sequence-length (two-eight digits) were presented until two repeatedly incorrect sequences of the same length occurred, at the most 14 presented trials.

The Rey Auditory-Verbal Learning Test

Fifteen unrelated concrete nouns were read aloud in five learning trials with an interval of 2 seconds (sec) between words. This series of words was presented five times. After each presentation immediate recall was tested. Twenty min after the fifth presentation, the number of words correctly recalled indexed long-term memory.

Instrumental Learning Task

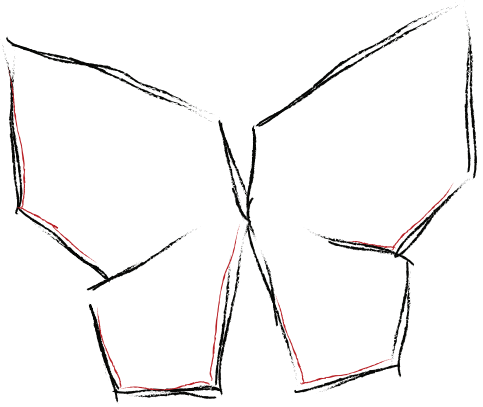
In this modified version, each trial involves the simultaneous presentation of a pair of cartoon-pictures. Children were required to choose between one of two stimuli: one associated with a high probability of obtaining feedback (70%) and the other with a low probability of obtaining feedback (30%). The task consists of two different pairs of pictures, each alone signifies the onset of one of 2 distinct trial types: reward or neutral. In the reward trials, positive feedback involved the presentation of a smiley and a point, whereas neutral feedback involved the presentation of a smiley alone. After 14 practice trials, two blocks, each containing 40 trials and two different sets of cartoon-pairs, were performed in a total duration of about 12 min. Children were encouraged to 'break the record' which was fictively set at 25 points (62.5% rewarded responses).

Time Reproduction task

In this task, two light bulbs were presented on the lateral sides of a computer screen. A trial started with the word 'kijk' ('look' in Dutch) displayed above the left light bulb for 3000 ms. Then the left light bulb turned yellow for different durations (4, 8, 12, 16, or 20 sec) in random order. As soon as the light bulb turned back to white, 'jouw beurt' ('your turn' in Dutch) were displayed above the right light bulb. This indicated that the duration of the stimulus had to be reproduced as accurately as possible by pressing a button for the same amount of time as the stimulus presentation, turning the right light bulb yellow. After release of the button, both light bulbs remained white for 1500 ms. After three practice trials, 20 experimental stimuli were presented in around 20 min. Children were not informed about the length of the intervals and did not receive feedback concerning their performance.

Time Production task

In this task, one-sec intervals had to be produced. After presentation of a fixation cross for 200 ms, an auditory tone of 800 Hz was presented for 50 ms. The end of the tone announced the start of the interval. Children were instructed to produce as accurately as possible the one-sec interval by pressing a button at the end of the one-sec interval. 1500 ms after the subject's response, visual feedback (1000 ms) was given, indicating whether the response was correct, too short, or too long. A response was correct, if it fell between the lower and upper boundary set by a dynamic tracking algorithm. Boundaries were set at 500 to 1500 ms at the beginning of the task. If the response fell within or outside these boundaries, the boundaries of the subsequent trial were respectively narrowed or widened by 100 ms. The task consisted of 10 practice trials and 80 experimental trials are administered. Before the task started a picture of a cartoon-cow was presented for one sec 10 times. Children were instructed to develop a strategy to 'get a feeling' of how long a sec is. These variables were created using MATLAB 7.5.



What future research should bring to help resolving the debate about the efficacy of EEG-neurofeedback in children with Attention-Deficit/ Hyperactivity Disorder

In recent years a rising amount of randomized controlled trials, reviews, and meta-analyses relating to the efficacy of EEG-neurofeedback in children with ADHD have been published, among which the studies described in **Chapter 3** and **4**. Although clinical reports and open treatment studies suggest EEG-neurofeedback to be effective, double blind placebo-controlled studies as well as a rigorous meta-analysis failed to find support for the efficacy of EEG-neurofeedback. Since absence of evidence does not equate with evidence of absence, we will outline how future research might overcome the present methodological limitations. To provide conclusive evidence for the presence or absence of the efficacy of EEG-neurofeedback in the treatment of ADHD, there is a need to set up a well-designed study that ensures optimal implementation and embedding of the training, and possibly incorporates different forms of neurofeedback.

Based on

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Introduction

ADHD is the most common neurodevelopmental disorder, affecting about 5% of all children worldwide. ADHD is characterized by a pattern of inattention and/or hyperactivity and impulsivity (Polanczyk et al., 2007).

While medication is the most effective treatment in ADHD (Faraone & Buitelaar, 2010), it also entails a number of concerns. Firstly, side effects have been reported and for some serious and life-threatening side effects, the risk is not clear and will likely remain so due to the rarity of these events (Graham et al., 2011). Children with ADHD and their parents also have significant reservations about possible negative long-term effects of medication (Berger et al., 2008). Secondly, there is insufficient evidence of long-term efficacy of medication for ADHD (van de Loo-Neus et al., 2011). Thirdly, the symptoms of ADHD have been found to reappear after discontinuing drug treatment (Jensen, P.S. et al., 2007; Murray et al., 2008). These misgivings about ADHD medications have contributed to the interest in developing non-pharmacological approaches to treatment, such as EEG-neurofeedback. EEG-neurofeedback is based on the rationales that (1) the neural basis of ADHD is characterized by deviant EEG patterns that play a role in the pathophysiology of the disorder; and (2) voluntary modulation of specific brain activity patterns can be learned by operant learning strategies. The first rationale originates from the finding that the majority of resting state EEG in children with ADHD is characterized by increased slow-wave activity (primarily in theta frequency range) and decreased fast-wave activity (primarily in beta frequency range). These slow and fast waves are often coupled, resulting in elevated theta/alpha and theta/beta power ratios (see Barry et al., 2003 for a review). Although a deviant theta/beta power ratio has been found in ADHD rather consistently (Arns, Conners, & Kraemer, 2013), the exact role of such a deviant pattern in the pathophysiology of ADHD is not clear yet (van Dongen-Boomsma, 2014). In addition, although voluntary modulation of specific brain activity patterns might be possible, clear-cut proof is still lacking. If these rationales are correct, they will provide for a rational neuroscience-based treatment of ADHD that brings about normalization of the underlying neural abnormality and thereby clinical improvement.

EEG-neurofeedback; the current state of affairs

In recent years, a number of randomized controlled trials, reviews, and meta-analyses relating to EEG-neurofeedback in children with ADHD have been published. Although particularly non-blinded studies conclude that EEG-neurofeedback is probably effective, robust evidence based on methodologically sound studies is still lacking. The majority of studies did not include a placebo group and/or blinded measures. Studies that did include a placebo group or a blinded design have not found superior effects of EEG-neurofeedback compared to placebo-NF (Perreau-Linck et al., 2010; Arnold et al., 2013; **Chapter 3**[1]). In addition, a systematic review and meta-analysis of randomized controlled trials (RCTs) of non-pharmacological interventions in children with ADHD including EEG-neurofeedback studies, reported non-significant results for the blind rating of symptoms (ES 0.29, $p = 0.07$; CI = -0.02, 0.61) (Sonuga-Barke et al., 2013). One of our previous studies (**Chapter 4**) did not find any effects at a neurocognitive level following EEG-neurofeedback treatment of ADHD participants. This chapter also included a systematic review of the extant literature which indicated that our findings were in line previous studies.

However, absence of evidence does not equate with evidence of absence. If EEG-neurofeedback truly has no effect, then the possibility of regulating brain activity via EEG-neurofeedback to improve ADHD symptoms can be refuted. Alternatively, a true effect of EEG-neurofeedback may be hidden by methodological flaws which would imply that the optimal way to apply or study this therapy is not yet known. Improvements in a number of different areas will be needed to overcome discrepancies in the EEG-neurofeedback literature. Firstly, improvements will be needed in study-design. Secondly, the implementation and embedding of the training may have to be improved. Thirdly, the assessment of other forms of neurofeedback, alongside EEG will also help to clarify outstanding questions. These three levels of recommendations will be discussed below.

1 The study by described in Chapter 3 describes behavioural data acquired from a project registered in the Clinical trial register under "Project ADHD and EEG-Neurofeedback THERapy"; **www.clinicaltrials.gov**; NCT00723684. Lansbergen et al. (2011b) describe the pilot data of this project. Chapter 4 described the neurocognitive data of this project and in addition provide a systematic review.

Study-design

While placebo-controlled RCTs are the gold standard in pharmacological research, there is no consensus regarding the optimal design for EEG-neurofeedback experiments.

Placebo-controlled RCTs

A major advantage of the inclusion of a placebo condition is that all aspects of both treatments are identical except for the underlying hypothesized working element. This enables allocation of positive findings to the working element only. Another advantage is that the amount of expectancy is equal between groups in contrast to all other control condition options, in which an equal amount of expectancy is difficult or even impossible to assess and correct for. The inclusion of a placebo condition also allows blindness of the child and parents, making blind assessments by proximal individuals possible. A common misconception of placebo-controlled RCTs which also exists in EEG-neurofeedback research (e.g., Heinrich et al., 2007; Gevensleben et al., 2012) is that it would be unethical to deprive participants of an effective treatment by allocating them to the placebo condition instead of the treatment condition. However, in cases where the efficacy of a treatment is not known and the purpose of the study is to determine if the treatment may be effective, then allocation of participants to a placebo group does not involve depriving a participant of treatment, as long as medication which a participant may be taking for his or her condition is continued during the course of the experiment.

A randomized placebo-controlled trial also has drawbacks, namely the fact that it is time- and energy- intensive, expensive, and may not be the strongest design for all interventions or settings (West & Spring, 2015).

Applying a randomized placebo-controlled trial design to EEG-neurofeedback experiments might create a selection bias. In certain cases, placebo-controlled RCT's may thereby limit the external validity of the findings (West et al., 2008). Only people that are willing to accept that they may be allocated to the placebo group will participate in the study. However, this problem may partly be alleviated by ensuring that participants that are taking medication continue their regime unaltered throughout the duration of the study. In addition, including a placebo condition may

make it more difficult to recruit participants due to a potential participant's reluctance to receive the placebo treatment. This can be (partially) overcome by conducting a multi-site center study and allowing ADHD medication to be used through the study period. Furthermore, lowering the expectancy by the possibility of allocation to the placebo group may make it more difficult for the treatment to have a positive effect of the treatment (like neuroregulation) (Gevensleben et al., 2009). In accordance, most participants of EEG-neurofeedback placebo-controlled RCTs conducted until now seem to experience the treatment as a placebo condition (Logemann et al., 2010; Lansbergen et al., 2011b; **Chapter 3** and **4**). One might speculate that this absence of efficacy is caused by reduced motivation of the participants or—on the other hand—from flaws in the protocol. The feasibility of the training should therefore be rated by evaluating EEG indices during the sessions of both groups (i.e., learning curves), in addition to measuring the guessing rate (i.e., how well parent and child were able to guess to what group they were allocated), as well as analyzing the differences between pre and post quantitative EEG measurements. Until now, of the randomized placebo-controlled trials, the study described in **Chapter 4** was the only study that evaluated EEG indices during the sessions and did not show any learning effect.

Generally, a placebo condition is only justified if the condition meets the following criteria. Firstly, the placebo condition must be inert with no possibility that this treatment trains a measurable physiological effect. This should be assessed by analyzing EEG indices during the sessions in the placebo condition. Secondly, all participants (i.e., the child, his/her parents, teacher(s)) as well as all examiners (i.e., the raters, but also the EEG-neurofeedback therapist) should be blinded. Due to technical restrictions in placebo- controlled studies it has not been possible to blind the therapist while implementing manual thresholding. However, the promising proposal by The Collaborative Neurofeedback Group (2013) has overcome these restrictions by creating a design in which real-time noise is superimposed on the placebo data creating the illusion of real time EEG recordings.

Alternatives to placebo-controlled RCTs

In relation to psychotherapy research, problems with the use of placebo-conditions have been emphasized (Borkovec & Sibrave, 2005). Clinical trials which attempt to eliminate unspecific treatment components by the use of placebo-conditions,

might give an inaccurate estimate of the clinical value of the treatment if nonspecific variables (e.g., expectations) interact with active treatment components. Jeopardizing treatment fidelity in such a way might also happen in EEG-neurofeedback. All problems discussed in relation to psychotherapy can certainly not readily be generalized to the research of EEG-neurofeedback in which the target of training is non-psychological in nature, in contrast to the psychological target psychotherapy has. Nevertheless, internal validity should not be readily assumed in either design. The external validity of alternatives to placebo-controlled RCT is often stronger than of placebo-controlled RCTs, but they also face a serious limitation in terms of ensuring internal validity (West et al., 2008). A number of promising alternatives to placebo-controlled RCTs, which attempt to overcome these difficulties, do exist. Disadvantages of performing a placebo-controlled RCT in certain situations and possible solutions to deal with them were elaborately discussed by West & Spring (2015). Their points and arguments on alternatives to placebo-controlled RCT's will be used further to discuss the use of such alternatives to study EEG-neurofeedback. When studying EEG-neurofeedback, the placebo condition can for instance be replaced with "additive comparison" or "treatment dismantling" in which aspects that are hypothesized to contribute to the efficacy of the treatment are added or left out of the treatment respectively. Alternatives to random assignment could be time-series, counterbalanced, cross-over and group randomized designs. These alternatives avoid unfair allocation and thereby circumvent a selection bias. "Partial blinding" is a method which allows for manual thresholding while minimizing the number of people that have to be unblinded. Another option is an "equipoise design" in which two treatments are equally well valued at the onset of the study which makes blinding less relevant.

A concrete example of an alternative approach to a placebo- controlled RCT for EEG-neurofeedback is "interrupted time series analysis" in which the treatment is introduced at different time points, but endpoints are equal (West et al., 2008). If the rater is unaware of the duration of treatment, the measurement can still be blind and expectancies of parents and children are controlled relatively well, i.e., they all receive the treatment that they expect to be effective. This design allows blind measures and comparable expectations in each group despite the lack of a placebo group. However, the design does assume that the amount of time spent on the training predicts the amount of improvement.

The optimal design

Regardless of the manner in which internal validity is maximized, the study-design can also be improved in other areas. For instance, the sample size should be in congruence with the power analysis, thereby enhancing the power and allowing more analyses (such as subtype analyses). In addition, the study-design should seek to determine whether or not EEG-NF is efficacious as a monotherapy or alternatively is valuable as an add-on therapy received in conjunction with medication. Although few studies to date have compared medication to neurofeedback (Duric et al., 2012; Meisel et al., 2013; Ogrim & Hestad, 2013), these studies struggled with major limitations and inconsistent findings. A more thorough comparison between medication and EEG-neurofeedback can be achieved by including additional subgroups that assess participants without medication together with participants on medication. A strong design should furthermore obtain objective measures of ADHD symptoms, e.g., by using school observations by an independent observer, actometers, or neurocognitive tests. Finally, a strong design should have an optimal implementation and embedding of the treatment, discussed further below. In summary, an improved design can be achieved by addressing the above mentioned points either through a placebo controlled RCT or an alternative design. Importantly, a design can only be optimal if reliable and valid outcome measures are selected and good quality control is maintained throughout data collection. Internal validity should be maximized while bias should be minimized (West & Spring, 2015).

Implementation and embedding of the training

EEG deviation

Most EEG-neurofeedback protocols focus on ADHD-related deviation in frequency bands during rest; up-regulation of theta power and down-regulation of beta power (Monastra et al., 2005). While the majority of children with ADHD exhibit diminished beta power, a subgroup of children with ADHD have been found to have excessive beta-power (Arns, 2012). Thus, the idea of repairing a deviate EEG pattern would not apply on these children without a personalized protocol.

Reward feedback

The percentage positive feedback that should be given has been under debate. Some researchers argue that for instance 80% positive feedback would to be too high for optimal learning (Arns, Heinrich, & Strehl, 2014). The percentage should not be too high not allowing sufficient learning, neither should the percentage be too low preventing a feeling of control. Consensus on what this percentage should be has not been reached and should be investigated.

Learning paradigms

To further improve the training, the development of a paradigm with instructions that are clearly goal-directed and in which the participant is encouraged to actively attempt to reach a certain "brain-state" might be more effective than strictly following an operant learning principle in which learning occurs through performance rather than through following a preceding intention. Creating awareness of the desired behavior might not only be more effective during training itself, but might also facilitate transfer into daily life since the participant is actively aware how to achieve a goal. Achievement of explicit goals might in addition enhance motivation. Since no placebo-controlled studies until now have been able to show specific treatment effects, a possible explanation besides design-related explanations discussed above, could be that a paradigm lacking clear instructions might not lead to a learned behavior being able to be incorporated in a participant's daily life.

Transfer

Without transfer of the (during treatment) learned skills into daily life, the usefulness of EEG-neurofeedback can seriously be questioned. To facilitate potential transfer effects into daily life, the following recommendations can be made. Explicit feedback on the deviation of oscillations might enable awareness of how to minimize this deviation, thereby creating a possibility to consciously prompt this minimization in any situation in daily life as well. This could be further strengthened by implementing transfer trials; a block within the training in which no immediate feedback is given. The participant is required to act as if immediate feedback is given at that moment, even though feedback is only given after the block has ended. In this way a daily life situation, in which no immediate feedback is provided either, is simulated more

realistically. The implementation of transfer trials has already been applied (e.g., Strehl et al., 2006; Drechsler et al., 2007; Heinrich, Gevensleben, & Strehl, 2007; Leins et al., 2007; Gevensleben et al., 2009, 2014), but has not been studied in a sufficiently well designed trial. Finally, transfer effects can be optimized by combining the pure EEG-neurofeedback sessions with sessions including behavioral therapeutic aspects to teach the participant to recognize daily life situations in which to apply the new skills learned from the EEG-neurofeedback (Heinrich et al., 2007; Gevensleben et al., 2009). Despite different aspects of EEG-neurofeedback that have been under debate as discussed above, a clear consensus of how the optimal implementation of EEG-neurofeedback should look like has not been reached.

Different forms of neurofeedback

Of course, the conventional EEG-neurofeedback is not the only alternative treatment for ADHD that could be studied. Different methods than the most popular most practiced resting state oscillatory EEG-neurofeedback could be scrutinized. Examples are online tomographic neurofeedback computed from multichannel scalp EEG (Liechti et al., 2012), real-time functional magnetic resonance imaging (fMRI) neurofeedback (Sulzer et al., 2013) or magnetoencephalographic (MEG) neurofeedback (Foldes et al., 2011). The advantage of tomographic neurofeedback is that more specific brain regions can be targeted due to the use of more electrodes. At least the same advantage can be reached when using MEG, without all the preparatory hustle that usually comes along with EEG. fMRI is of course spatially even more precise but deals with a temporal delay of measurement. Both MEG and fMRI based neurofeedback are far more expensive than EEG; however difference in costs may be less when only a few sessions are needed. Studies have shown that all these methods are feasible, each having its own advantages and disadvantages. All these methods seem to outperform conventional EEG-neurofeedback since they allow more direct feedback, based on more specific brain structures.

When sticking to the EEG-neurofeedback protocol or more specifically to a personalized EEG-neurofeedback protocol, it can be questioned how deviations should be determined. Children in the active group of our study received a personalized protocol, but EEG data recorded during the sessions showed that not all desired training directions were met (**Chapter 4**). Significant improvement on group level

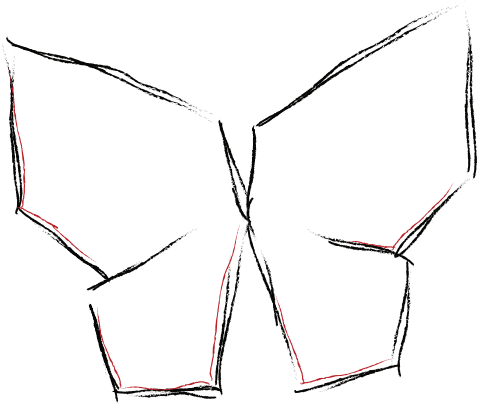
can only solidly be interpreted if all training conditions hypothesized to improve ADHD (either on behavioral or neurocognitive level) are actually improved in the desired direction. Determining deviations during rest might differ from deviations during task performance. Generalization to daily life might be greater when the neurofeedback is based on EEG deviations during task performance. The most often replicated EEG-deviation in ADHD has been shown at rest (Arns, Conners, & Kraemer, 2013), but does not show an unambiguous relationship with behavioral and cognitive performance (**Chapter 3**). Still, the existence of a straightforward relationship between these two is the basis of the conventional EEG-neurofeedback therapy. Since dysfunction due to the ADHD core-symptoms is primarily experienced during cognitive or motor activity, a focus on electrophysiological indices during activity may have a better rationale than during rest. In addition, generalization to daily life (hence, transfer) might be greater when the neurofeedback is based on EEG deviations during task performance. These arguments plead for real-time deviation determined during interactive task performance. A clear example of such an application of neurofeedback (in healthy individuals) is by real-time training alpha oscillations during task performance in an MEG scanner (e.g., Jensen et al., 2011).

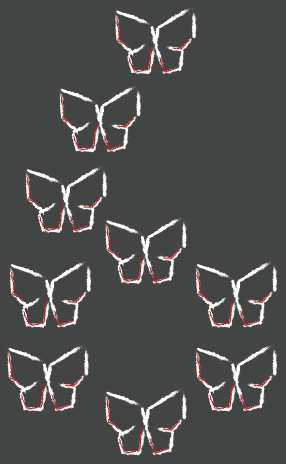
In the early days, alpha enhancement neurofeedback (6 – 13 Hz) protocols failed to find a specific effect on hyperkinetic behavior (Nall, 1973). After this starting point, the alpha frequency band has not been the focus of neurofeedback. Nevertheless, alpha activity is associated with active inhibition of brain areas, which is hypothesized to result in allocation of attention (Klimesch et al., 2007). Aberrant modulation of alpha activity during task performance has been associated with attention problems on clinical level (i.e., adults with ADHD) (ter Huurne et al., 2013). Hence, a relationship has actually been shown between behavioral measures (to what extent the cue induced allocation of attention) and alpha oscillations (the lateralized difference in alpha power expected due to allocation of attention following the inhibition notion) in ADHD. In addition, the height of the alpha frequency peak has been shown to be lower in a subgroup of children with ADHD (**Chapter 2**) and predictive to treatment outcome of several treatments (Ulrich et al., 1984; Arns et al., 2008, 2009, 2013; Arns, 2012). Different characteristics of the alpha frequency band therefore seem to be relevant to ADHD. It is worthwhile to further investigate neurofeedback possibilities training this frequency band. These results could be related to the neurophysiological substrate of the disorder. To study this active inhibition notion, active task involvement is necessary implying interactive task performance. By improving the therapy with

suggestions mentioned above, other forms of neurofeedback might also have potential as treatment for ADHD.

Conclusion

The debate whether EEG-neurofeedback is an effective treatment for ADHD can be closed by setting up an optimal study with a study-design that tackles the drawbacks of a randomized placebo-controlled trial design that are consequential to studying EEG-neurofeedback while keeping blind measurements and avoiding other ways of desecrating the internal validity. In addition, EEG-neurofeedback should be implemented in an optimal learning setting both on the technical level of the EEG-neurofeedback and with respect to embedding of the learning strategies into daily life. Finally, alternative forms of neurofeedback to conventional EEG-neurofeedback, may offer other, maybe even better, promising alternatives.





Lateralized modulation of posterior alpha oscillations in children

In **Chapter 5** it was suggested that the alpha frequency-band should be investigated further in relation to ADHD, especially during task performance. The evidence for a functionally inhibitory role of alpha oscillations is growing stronger, mostly derived from studies in healthy adults investigating spatial attention. It remains unexplored if the modulation of alpha band oscillations plays a similar functional role in typically developing children. The current chapter focused on the characterization of alpha modulations in children in relation to attentional performance. To investigate this, the posterior alpha activity (8 – 12 Hz) in children between 7 and 10 years old was measured using EEG while they performed a visuospatial covert attention task.

We found that the alpha activity decreased in the hemisphere contralateral to the attended hemifield, whereas it relatively increased in the other hemisphere. In addition, we found that the degree of lateralized alpha modulation predicted performance on the attention task by negatively predicting the response time on invalid trials. Of note, children who were behaviorally less influenced by spatial cueing also were children with a clear lateralized alpha modulation pattern, with a significantly stronger alpha lateralization in the left hemisphere than children who were influenced more by spatial cueing. In addition, a bias to the right visual field such as that commonly observed in children, was significantly smaller or absent in the children influenced least by spatial cueing. Among all children, the magnitude of this visual field bias was positively related to the ability to modulate alpha activity.

In conclusion, we have shown that the pattern of alpha oscillations modulated by attention is already present in 7 – 10 year old typically developing children. Although a similar pattern is observed in adults, the consequences for behavior are different. The fact that alpha modulation is already present at this age opens up the possibility of using hemispheric alpha lateralization as a tool to study the physiological basis of attention deficits in clinical disorders such as ADHD.

Based on
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Introduction

Allocation of attention requires a focus on relevant and simultaneous suppression of irrelevant information (Posner & Petersen, 1990). Increasing evidence has demonstrated that allocating spatial attention is associated with regional specific modulation of alpha oscillations (8 – 12 Hz). These oscillations have been suggested to gate streams of information through the brain network by means of functional inhibition (Klimesch, Sauseng, & Hanslmayr, 2007; Thut & Miniussi, 2009; Snyder & Foxe, 2010), a process described by the 'alpha inhibition hypothesis' (Jensen & Mazaheri, 2010). The functional role of alpha activity in healthy adults has particularly been studied using visuospatial covert attention cueing paradigms based on variations of Posner's paradigm (Posner, 1980). In most electroencephalography (EEG) and magnetoencephalography (MEG) investigations of covert spatial attention, a cue directs attention to the left or right visual hemifield, which allows for investigating the alpha power in the hemispheres processing the attended and unattended visual hemifields. The key finding is that posterior alpha power increases ipsilateral and decreases contralateral to the attended visual hemifield, respectively inhibiting or facilitating the information flow (Worden et al., 2000; Sauseng et al., 2005; Kelly et al., 2006; Thut et al., 2006; Händel, Haarmeier, & Jensen, 2011; Bengson, Mangun, & Mazaheri, 2012; ter Huurne et al., 2013). High alpha power over task-irrelevant regions linked to the processing of the unattended information, has proved to be of crucial importance for optimal attentional performance (Romei, Gross, & Thut, 2010; Händel et al, 2011). Whether similar modulations of posterior alpha power can be observed in children is not known yet.

While rudimentary forms of attentional functions are already present at birth and further develop during the very first year of life (Colombo, 2001), the ability to allocate attention keeps developing throughout childhood (Rueda, 2013). For instance, orienting of attention seems to improve from 6 or 7 years onwards by gaining the ability to disengage attention when necessary (Schul, Townsend, & Stiles, 2003; Wainwright & Bryson, 2005). The fully developed attentional network has been proposed to involve two main systems: 1) a largely bilateral dorsal fronto-parietal system that is involved in goal-directed stimulus response selection, and 2) a right-lateralized ventral system, that directs the attention to salient unexpected stimuli. The ventral system is thought to work as an alerting mechanism engaging the dorsal system when unexpected stimuli are detected (Corbetta & Shulman, 2002). We propose

that in Posner's cueing paradigm, the dorsal system enables early orienting towards a cued location and the ventral system is required for shifting attention towards 'surprise' targets in the uncued hemifield. According to the alpha inhibition hypothesis, we would be able to measure lateralized alpha modulation during the preparation interval, when goal-directed allocation of attention is expected. It is unclear whether children display lateralized posterior alpha modulation with spatial attention similar to adults and whether changes in alpha power relate to behavioral performance. The aim of this study was to investigate how alpha modulations observed in children relate to previous observations in adults. To this end, we investigated the modulation of oscillatory brain activity as recorded by EEG in relation to behavioral performance of 7 to 10 year old typically developing children performing a visuospatial covert attention task.

Materials and methods

Participants

Data were acquired in the context of a clinical trial investigating alpha oscillations in children with and without ADHD (ClinicalTrials.gov identifier NCT01932398). The study was approved by the local Medical Ethics Committee (http://www.cmoregio-a-n.nl/) and conducted in accordance with the Declaration of Helsinki. All parents gave written informed consent, children gave oral assent. Here we reported information relevant to the present study only, focusing on typically developing children, i.e. not the children with ADHD. Children in the age range from 7 to 10 years old were recruited from primary schools in the area of Nijmegen, the Netherlands. Children were included if they never had a psychiatric, neurological, or cardiovascular disease or serious motor or perceptual handicap; and if their estimated IQ was above 80. If an intelligence test had not taken place over the past two years, two subtests (i.e. Vocabulary and Block Design) of the Wechsler Intelligence Scale for Children (WISC-III; Wechsler, 1991; Dutch version: de Kort et al., 2002) were administered to estimate the intelligence. The Child Behavior Checklist (CBCL; Verhulst, van der Ende, & Koot, 1996) was used to rule out the presence of clinical behavior. Data were collected between April 2012 and June 2014. Parents received reimbursement for travel costs and children received a present. Twenty-seven right-handed children were included in this study. Data from three children were excluded (N = 2 technical problems,

N = 1 task performance below chance level). Three other children were identified to have very few correct responses on the invalid trials (10.2 ± 15.9%). Data from these children were rejected for further analyses because 1) it was not possible to calculate behavioral performance on invalid trials and the subsequently derived cueing effect based on response time (RT) for these children since RTs for invalid trials were lacking, 2) these children responded significantly faster (N = 3: 262.61 ± 31.14 ms) on the available valid trials than the other children (N = 20: 571.22 ± 104.59 ms) ($t(21) = 4.987$, $p = .001$), suggesting they used a different strategy. Final analyses were therefore conducted using data of the remaining 21 children (mean age, 9.11 ± 1.29; 42.9% boys; estimated IQ, 119.23 ± 17.63).

Study procedure

All measurements were performed at the Donders Centre for Cognitive Neuroimaging, Nijmegen, the Netherlands. Children and their parents visited the institute twice. First, if not available, intelligence was estimated. Furthermore, the first visit was used to explain and practice the visuospatial covert attention task, subsequently referred to as *the attention task*. This practice session was conducted while tracking the eyes to train the children to keep fixated at the center, but without EEG measurement. During the second visit the attention task was performed while tracking the eyes and recording the EEG. In addition, two resting state EEG sessions, in which the child was instructed to sit quietly for 2 min with eyes open and 2 min with eyes closed, were recorded during the second visit. Analyses of these data are not presented here.

The attention task

An adjusted version of Posner's cueing paradigm for spatial orienting of attention was used (Posner, 1980), in which the goal was to save a fish from being eaten by a shark (*Figure 1*). The task was programmed and presented using the software package Presentation (Neurobehavioral Systems, Albany, CA). The task started with a 1 min introduction video in which a shark recapped the most important instructions. Trials started with a pre-cue period (500 ms) with a shark presented at each side of the screen and a fish presented centrally. The child viewed the screen from a 50 cm distance creating an angle of 5.5 degrees with the innermost edge of the target figures. Note that the most informative part of the target was between the edge

(5.5 degrees) and the middle of the target figures (13.1 degrees). The child was instructed to fixate at the fish in the middle of the screen and to sit as quietly as possible throughout the task. Influences of movement on the eye tracker and EEG recordings were shown to the child in advance to illustrate the importance of sitting still. An attentional cue was presented in a 200 ms interval, in which the fish shifted gaze towards the left or the right shark indicating the side of the upcoming target if validly cued or indicating the opposite side if invalidly cued. In the next period (1000–1500 ms jittered) the child was expected to prepare for the upcoming target, hence this period was referred to as the *preparation period*. Next, the sharks both opened their mouths (100 ms), the target being the shark with the widest mouth. The child had to press the left or right button with the right index or middle finger to indicate the left or right shark, respectively. Correct responses had to be delivered within 1400 ms after target presentation to prevent negative feedback. Depending on the button press, positive or negative feedback was then presented for 500 ms, consisting of a happy fish or a fish bone, respectively. As encouragement a short task-related video with a shark was shown after every 37 trials. During the first visit, the child practiced 100 trials (40 valid trials and 10 invalid trials per visual hemifield). Hence, the cue predicted the target location in 80% of the trials. During the second visit, the task consisted of 368 trials (138 valid trials and 46 invalid trials per visual hemifield). Hence, the cue predicted the target location in 75% of the trials. The correct prediction of the cue was set higher in the practice session to stimulate the child to use the cue information while learning the task. The left or right cue occurred with equal probability.

Eye tracking

Eye gaze was calibrated using a corneal reflection eye tracker and ClearView software (Tobii 1750, Tobii Technology Sweden), recording both eyes. Following a five point calibration procedure, the eye tracker made it possible to monitor fixation during the pre-cue and preparation period. During the pre-cue period, the cue was presented only when the child fixated on the screen center. If not fixating during the subsequent preparation period, three different types of instruction videos were presented immediately depending on the size of the deviation from the middle. It gave instruction to fixate on the eyes of the fish (small deviations), to fixate on the fish (median deviations), or to not look at the sharks (large deviations).

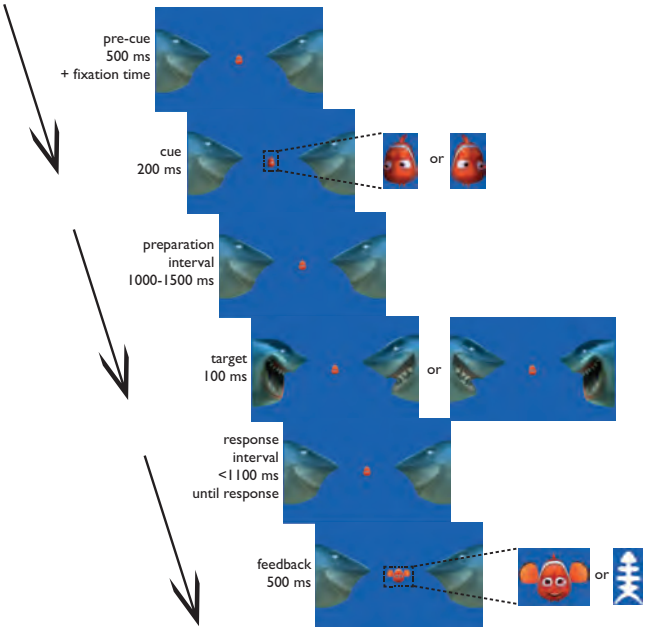


Figure 1. The attention task. After a neutral pre-cue period in which a fish and two sharks were presented on the screen, children were cued to attend to the left or the right visual hemifield while keeping fixation at the centrally presented fish. After a 1000 – 1500 ms preparation interval, both sharks opened their mouths; one more so than the other. Children had to report which shark had the widest opened mouth. In 75% of the trials the widest opened mouth was in the cued visual hemified (valid cue trial), whereas in 25% surprise trials the mouth was widest opened in the other hemifield (invalid cue trial). Following a correct response within the response interval, a happy fish was presented. For incorrect responses, the fish was replaced by a fishbone.

EEG recordings

The EEG was recorded continuously during a 2 min eyes-open and a 2 min eyes-closed resting-state condition, and during the attention task. It was recorded from 32 scalp electrodes placed according to the 10 – 20 system using the actiCAP and BrainAmp system (Brain Products GmbH, Munich). The vertex (electrode between Cz and Fz) was used as online reference; offline the data were referenced to the average of all electrodes. Electrode Fpz was used as ground. Electrode impedance was kept below 20 kOhm. The data were sampled at 500 Hz following a 0.016 Hz high-pass and a 125 Hz low pass filter. The gain was set to 0.1 μV resolution per bit.

Analyses

Data were processed and analyzed using MATLAB 2012a (The MathWorks, Inc., Natick, MA) and the FieldTrip analysis toolbox (http://fieldtrip.fcdonders.nl). When

correlation analyses were performed, these were always tested non-parametrically using a Spearman correlation test.

Behavioral performance

RTs were expected to be distributed as an exponentially modified Gaussian (ex-Gaussian) distribution, implying that RTs contained a mean (mu) and standard deviation (sigma) of a Gaussian component and a mean (tau) of the exponential component (Lacouture & Cousineau, 2008). We expected that cueing effects would be reflected by changes in mean of the Gaussian component rather than in the exponential component of the ex-Gaussian distribution. Therefore, all RT analyses were conducted using the mu of RT ex-Gaussian distribution. Furthermore, RTs faster than 100 ms were considered too short to reflect stimulus perception (Luce, 1986), while RTs larger than 4 times the standard deviation of the mean were regarded outliers (Schmiedek et al., 2007). These trials were therefore rejected from behavioral analyses. Cueing effects in hit-rates were also analyzed.

Spectral analysis of the EEG data

Data segments showing artifacts such as muscle potentials, and amplifier or electrode noise, were identified using a semiautomatic routine and excluded from further analyses. An independent component analysis was used to detect and remove component(s) with electrooculographic origin, using a fastica algorithm (Hyvärinen, 1999). The EEG recordings were bandpass filtered at 2 – 30 Hz. Only trials in which the child fixated were used for further analysis. Fast Fourier Transform, with a time-window of T = 5 cycles (T = 5/f) and a Hanning taper, was used to calculate time-frequency representations of power (2 – 30 Hz, with a frequency resolution of 2 Hz). The time interval was either cue-locked from −0.25 to 1.5 s around cue-onset or target-locked from −1 to 0.2 s around target-onset. The alpha modulation index (MI) from cue-locked data was used to investigate whether a task-based modulation could be observed in the alpha band (8 – 12 Hz). The MI was computed by subtracting alpha power of right-cued trials from left-cued trials for each electrode. This subtraction was subsequently normalized by dividing by half of the sum of these values:

$$MI = \frac{(alpha_{left\ cued\ trials} - alpha_{right\ cued\ trials})}{\frac{1}{2}\ (alpha_{left\ cued\ trials} + alpha_{right\ cued\ trials})}$$

The MI was averaged over a-priori chosen left (left MI) and right (right MI) hemisphere parietal and occipital electrodes (left: P3, PO9, O1; right: P4, PO10, O2). From these values we constructed a combined MI (left MI minus right MI). A cluster based permutation test was performed to identify time clusters for which the left MI differed significantly from right MI (van Ede et al., 2011). This test controls multiple comparisons by identifying significant clusters of time points rather than significant individual time points over the time-interval (-0.2 to 1.5 s). The longest significant time cluster was used for further analyses. Similar analyses were conducted for target-locked data (time interval −1 to 0.2 s).

Results

The visuospatial covert attention task performed by the 21 children is shown in *Figure 1*. The fish in the middle cued the children to attend to the left or the right shark. After a preparation interval (1000 – 1500 ms), both sharks opened their mouth and the children had to indicate with a button press which of the two sharks opened their mouth the widest. In 75% of the trials, the cued shark did.

Behavioral performance

All children completed the task consisting of 368 trials. After rejection of trials where fixation was lost and trials containing artifacts, 176 ± 29 trials remained for EEG-analyses. Of these, in 44 ± 8 trials the target was invalidly cued. The RT distributions were fitted to an ex-Gaussian distribution (for example, see supplementary material *Figure A1*). All further analyses were therefore conducted using mu, which represents the mean of the RTs when controlling for the exponential component of the distribution. As expected, children responded faster to validly cued targets (461 ± 94 ms) than invalidly cued targets (517 ± 103 ms) resulting in a statistically significant cueing effect (paired t-test, $t(20)=-6.98$, $p = .001$). The cueing effect was also observed when considering hit-rates; children were significantly more accurate on validly cued targets (94.34 ± 7.79%) than invalidly cued targets (90.99 ± 12.41%) ($t(20) = 2.51$, $p = .02$). The magnitude of the RT cueing effect was not significantly related to age ($r = .301$, $p = .186$), nor was the hit-rate cueing effect ($r = -.038$, $p = .872$). Since the cueing effect was more variable over children when considering RTs, this behavioral measure was chosen for further analyses.

Modulation in the alpha band

To study hemispheric modulation of oscillations following the cue initiated allocation of attention in children, we contrasted the spectral power for left versus right cues for each hemisphere separately and in combination. Time-frequency representations of power for left cued trials minus right cued trials, normalized by their mean and averaged over left (*Figure 2a*) and right (*Figure 2b*) occipital and parietal electrodes demonstrated a clear modulation mainly constrained to the alpha band. The alpha power decreased in electrodes contralateral to the cue while it relatively increased in ipsilateral electrodes. Note the modulation observed around the cue-onset (*Figure 2a*). This modulation was however not significant ($t = -0.1$ to 0.1 ms interval tested). This was also confirmed when directly comparing left and right electrodes (*Figure 2c*, bottom panel). When combining the modulation in the alpha band (8 – 12 Hz) by subtracting the left and right hemisphere MI (*Figure 2c*, top panel), it became clear that the modulation with attention was most pronounced ~0.6 s after cue-onset. A permutation test controlling for multiple comparisons over time verified that left and right MI in the alpha band significantly differed from each other and that this difference was most pronounced in the interval 0.50 – 1.05 s after cue-onset ($p = .002$) (indicated by the dashed square, top panel). Data was then averaged over these time points and the alpha frequency band, and finally over participants, to create a topographic representation (*Figure 2d*). We observed that the modulation in the alpha band was stronger over occipital and parietal electrodes. Similar analyses were performed for data that were time-locked to the target-onset. Visualization of these data is shown in the *Target-locked results* in the appendix of this chapter (*Figure A2*). A time cluster permutation test revealed one significant cluster in the period 0.95 – 0.50 s before target onset ($p = .002$). This time-window overlapped with the interval identified in the cue-locked data. In short, we have demonstrated that, as in adults, posterior alpha band activity is robustly modulated by spatial attention in children.

Alpha modulation and behavioral performance

We subsequently asked whether the ability to modulate alpha activity correlated with attentional performance. Hence, we correlated the combined cue-locked MI in the alpha band (0.50 – 1.05 s) with the RT cueing effect (mu for valid compared to invalid targets). Contrary to our expectations, we did not observe a significant correlation ($r = -.331$, $p = .143$). The direction of this relationship was opposite to

that found in ter Huurne et al. (2013) (*Figure 3a*). Although a relationship between RT on valid trials and combined alpha MI was absent ($r = -.355$, $p = .115$) (*Figure 3b*), a faster response to invalid trials was related to stronger MI ($r = -.468$, $p = .034$) (*Figure 3c*). The child that seemed to have an atypical response (high MI and fast RT) was not rejected since our criterion for rejecting participants (see *Method* section of this chapter) was not applicable. The rejected children described in, the *Participants* section of this chapter, had 10.2 ± 15.9% correct answers on invalid trials, while this particular child had 42.3% correct answers on invalid trials.

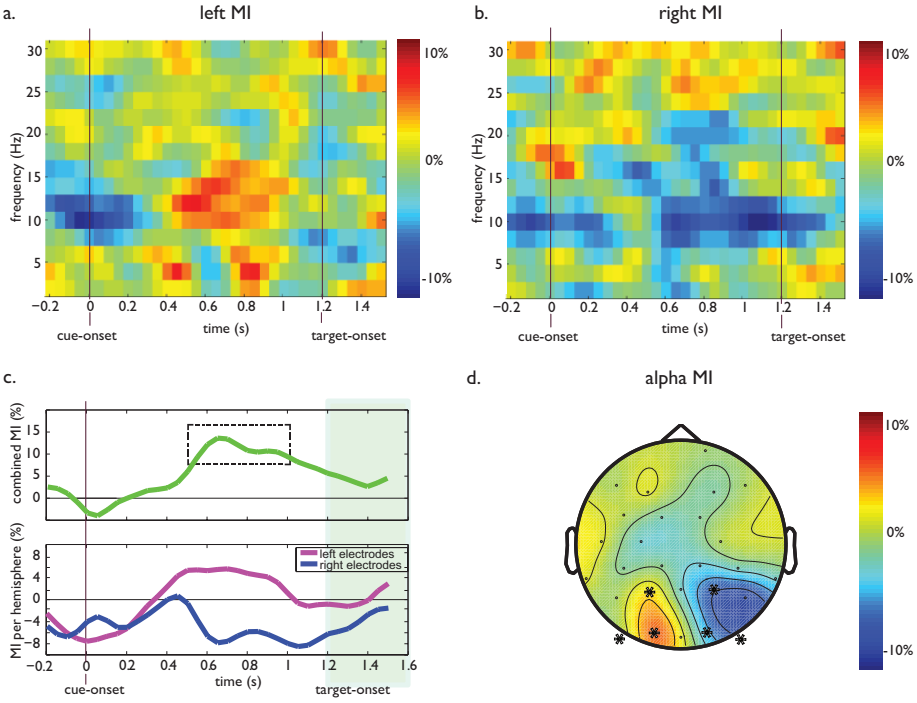


Figure 2. The modulation of alpha band power in response to the spatial cue. (*a*). Time-frequency representation of the MI (normalized modulation in power for left minus right cues) averaged over children in left occipital and parietal electrodes. The alpha power was stronger for left (ipsilateral) compared to right (contralateral) cues. The vertical line at zero represents cue onset. The vertical line at t = 1.2 s represents the first possible target-onset. (*b*). Similar to a, for right electrodes. The alpha power was weaker for left (contralateral) compared to right (ipsilateral) cues. (*c*). (Top panel) Time-course of the combined MI (left electrode MI minus right electrode MI) averaged over children (occipital and parietal electrodes), in the 8–12 Hz alpha band. The dashed square indicates the time cluster for which the MI in left electrodes and right electrodes differed significantly (t = 0.50–1.05 s; $p = .002$) from each other. The vertical line at zero represents cue onset. The green area indicates the jittered possible onsets of the target presentation (last possible onset at 1.7 s). (Bottom panel) Time course of the left MI and right MI separately. (*d*). Topographic representation of the MI averaged over children, in the alpha band (t = 0.50–1.05 s). The alpha power that is clearly lateralized with respect to the spatial cue appears restricted to the posterior electrodes. Stars indicate the selected channels for further analyses.

Abbreviations: MI: Modulation Index; Hz: Hertz; s: seconds.

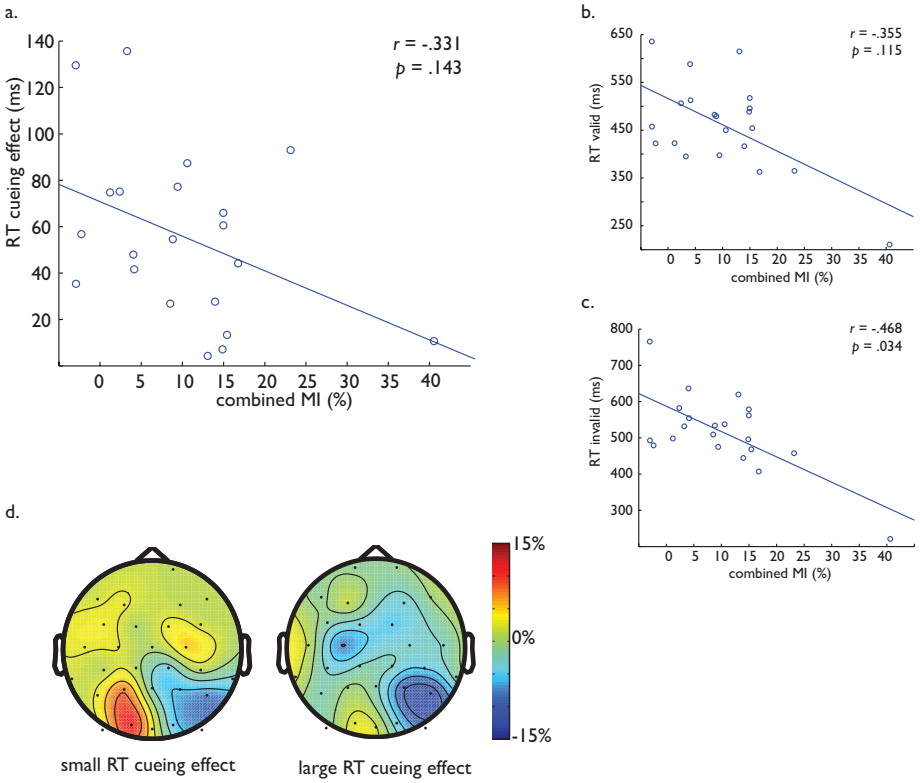


Figure 3. Relating the modulation of alpha power to attentional performance. (*a*). The relationship between the combined MI in the alpha band and the RT cueing effect ($r = -.331$, $p = .143$). The RT cueing effect was defined as the mu on invalidly cued trials minus the mu on validly cued trials (b&c). The relationship between the combined MI in the alpha band and the RT on (*b*) valid trials ($r = -.355$, $p = .115$) and on (*c*) invalid trials ($r = -.468$, $p = .034$). (*d*). Topographic representations of the MI in the alpha band (t = 0.50 – 1.05 s) for children with a small and large RT cueing effect.

Abbreviations: MI: Modulation Index; Hz: Hertz; s: seconds; RT: Response Time.

We further investigated the relationship between alpha MI and attentional performance by separating the children in two groups according to the cueing effect observed in the RTs. We found that in children with a small cueing effect (N = 11), the topographic representation of the MI was pronounced (*Figure 3d*, left), but no clear lateralized modulation was observed in children with a large cueing effect (N = 10) (*Figure 3d*, right). These groups significantly differed from each other with respect to MI in the left hemisphere ($t(19) = 2.482$, $p = .023$) but not right ($t(19) = 0.339$, $p = .738$). When considering the target-locked data, we confirmed the absence of a significant correlation between the combined MI in the alpha band

and the RT cueing effect ($r = -.313, p = .167$) as well as between combined alpha MI and valid trials RT ($r = -.304, p = .180$). We did not confirm a relationship between mu RT on invalid trials and alpha MI ($r = -.364, p = .106$). We conclude that children that modulate the posterior alpha band activity the strongest are children that are influenced least by the spatial cueing, most likely having the least difficulty with an unexpected switch of attention. However, children with a small cueing effect (489 ± 112 ms) were not significantly faster on invalid trials than children with a large cueing effect (547 ± 89 ms) ($t(19) = -1.287, p = .214$), nor were they slower on valid trials (small cueing effect group: 461 ± 109 ms, large cueing effect group: 461 ± 80 ms, $t(19) = 0.000, p = 1.00$).

The influence of a right visual hemifield bias

Since children are known to display a bias towards the right visual hemifield (Takio et al., 2013) in contrast to adults who display a bias to the left visual hemified (Bowers & Heilman, 1980; Manly et al., 2005), we investigated the presence of such a bias and its relation to the ability to modulate alpha activity. In our sample, children were indeed significantly faster ($t(20) = 2.091, p = .049$) on valid trials cued to the right visual hemifield (453 ± 96 ms) compared to the left visual hemifield (468 ± 94 ms). This difference was not apparent for the invalid trials ($t(20) = 0.488, p = .631$). We then created a measure representing the hemifield bias termed the Cueing Effect Hemifield Index (CEHI): the right cueing effect versus the left cueing effect, i.e., the cueing effect for right responses minus the cueing effect for left responses. There was a strong trend towards a faster cueing effect in the right hemifield than in the left hemifield ($t(20) = 2.050, p = .054$). Interestingly, when a median split was performed based on RT cueing effect (same groups as *Figure 3d*), children who displayed a small cueing effect did not show a significant CEHI ($t(10) = -0.144, p = .889$) while children who displayed a large cueing effect clearly did show a significant CEHI ($t(9) = 3.267, p = .010$). When these groups were compared on CEHI using a two sample t-test, a significant difference was found ($t(19) = 2.64, p = .016$); children with a large RT cueing effect had a rightward bias (CEHI: 43 ± 13 ms) while children with a small RT cueing effect had not (CEHI: −2 ± 11 ms). The CEHI was not significantly correlated with age ($r = -.118, p = .609$). Next, we queried whether there was a relationship between the alpha MI and the behavioral CEHI. We found no significant correlation between the combined MI in the alpha band and the CEHI ($r = -.216, p = .346$). However, when considering the hemispheres separately, the

left electrode MI showed a significant correlation with CEHI ($r = -.487$, $p = .027$): children with a diminished ability to modulate alpha activity in the left hemisphere displayed a stronger bias to the right visual hemifield. (*Figure 4a*). For the right MI, no such correlation was found ($r = -.175$, $p = .445$) (*Figure 4b*). All in all, we found that a smaller rightward bias was related to a stronger ability to modulate alpha activity in the left hemisphere as well as to making less use of the spatial cueing. However, rather than predicting the expected cueing benefit, posterior alpha modulation negatively predicted the response time on invalid trials. This finding is a surprise given that studies in adults found, the reverse relation (ter Huurne et al., 2013).

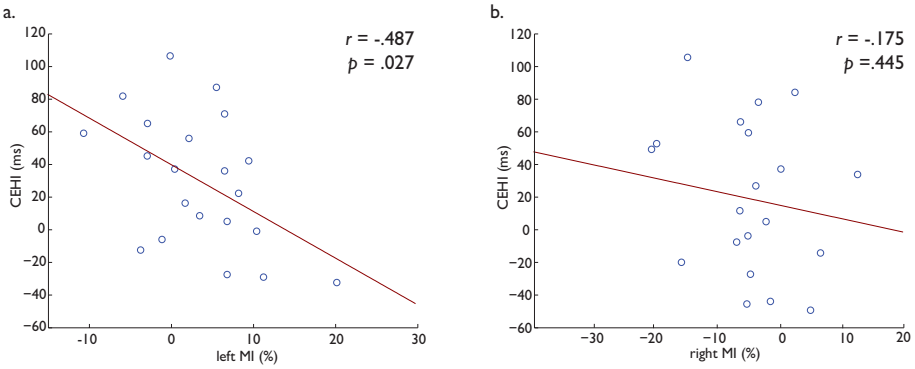


Figure 4. The alpha modulation index per hemisphere in relation to bias in cueing effect hemifield index. (*a*). Relationship between left electrode MI in the alpha band and the right cueing effect minus the left cueing effect. (*b*). Similar to (*a*) but for the right MI.

Abbreviations: CEHI: Cueing Effect Hemifield Index; ms: milliseconds; MI: Modulation Index. *r*: coefficient of correlation. *p*: probability value.

Discussion

The current study investigated the modulation of alpha band activity in 7 – 10 year old typically developing children performing a visuospatial covert attention task while EEG was recorded. We found that the alpha power (8 – 12 Hz) decreased in the hemisphere contralateral to the attended hemifield, whereas it relatively increased in the other hemisphere. This pattern was consistent with what studies previously found in adults (Worden et al., 2000; Sauseng et al., 2005; Kelly et al., 2006; Thut et al., 2006; Händel et al., 2011; Bengson et al., 2012). In addition, we found a relationship between the posterior alpha modulation and attentional performance. However, rather than predicting the expected cueing benefit, posterior alpha modulation

negatively predicted the response time on invalid trials. This finding is a surprise given that studies in adults found the reverse relation (ter Huurne et al., 2013). Children with a large cueing effect showed significantly less left hemisphere alpha modulation than children with a small cueing effect. Furthermore, children with a large cueing effect were those that displayed a significantly stronger bias to the right visual field. The magnitude of this rightward bias was negatively correlated with left hemisphere alpha modulation. A rightward bias is thought to change as a function of age, being more common in children and elderly than in young adults (Takio et al., 2013). All in all, an increased ability to modulate alpha activity in either or both hemispheres was associated with a smaller cueing effect and a diminished rightward visual bias. We quantified the relationship between the alpha modulation and behavior for both cue-locked and target-locked behavior. The rationale for examining the target-locked alpha modulation was based on results shown by ter Huurne et al. (2013). This study showed a lack of maintenance of the alpha modulation during the preparation interval in adults with ADHD and also showed a different relationship of alpha lateralization preceding the target to behavioral performance between adults with and without ADHD.

Since the healthy children from the current sample showed a bias to the right visual hemifield similar to adults with ADHD (ter Huurne et al., 2013), we additionally investigated alpha activity preceding the target. In general the relationship was stronger in these healthy children for the cue-locked alpha modulation compared to target-locked. This is partly explained by the target-onset being jittered in time. It also means that the 'attentional state' as reflected by the alpha band activity was coordinated by the cue rather than the anticipation of the target. Although based on previous results in adults we would have expected alpha modulation to be stronger along with the ability to allocate attention, i.e. along with the cueing effect (ter Huurne et al., 2013), we did not find such a relationship. We even found that lateralized alpha modulation was more pronounced in children with a small rather than large cueing effect. One interpretation of these results would be that alpha activity in the posterior brain areas in children is not predictive of inhibition of the visual stimuli, inconsistent with the alpha inhibition hypothesis. Following this interpretation the functionality of alpha activity might change during the course of development. The results might however also be explained from a broader developmental perspective. That is, while developmental improvement of alertness (Berger et al., 2000) and orienting (Schul et al., 2003) may decrease response times of valid cues, the developmental

facilitation of attention disengagement may decrease response time following invalid cues even more, hence reduce the difference between invalid and valid trials (Schul et al., 2003). This would mean that a cueing effect decreases with the increased ability to disengage attention, i.e. with development. Since attention disengagement is thought to be related to the stimulus-driven ventral stream while the top-down dorsal system is thought to be most strongly related to goal-driven preparation, alpha modulation – influenced by frontal structures known to be part of the dorsal system (Marshall et al., 2015b; Sadaghiani et al., 2010; Zumer et al., 2014) – could be hypothesized to be present independent of the ability to disengage attention. However, the two networks are not thought to work in isolation, but to interact in a flexible manner (Vossel, Geng, & Fink, 2014). A smaller cueing effect due to improved attention disengagement in these developmentally crucial years may be somewhat separate from a relationship between alpha modulation and attention allocation. Still, a suboptimal interaction between and/or a slower development of both the dorsal and ventral attention networks might explain a less clear alpha modulation pattern in children with a large cueing effect (i.e. less disengagement of attention). It might also explain the subtle relationship that we found between RT on invalid trials and alpha modulation, since disengagement of attention is needed in response to the invalid trials. Children with a large cueing effect had a significantly larger bias to the right visual hemifield than children with a small cueing effect. A study that investigated both attention disengagement and biases showed that the youngest children (6 years old) both had attention disengagement problems and showed a bias to the right visual hemifield whereas both of these effects were reduced in the older children (Wainwright & Bryson, 2005). This might suggest that a developmental shift in attentional bias co-occurs with improvement of attention disengagement. In addition, a significant negative correlation between the rightward bias magnitude and left hemisphere alpha modulation may be in line with the notion that alpha modulation is related to attentional performance. A rightward bias is not only seen in children (Takio et al., 2013), it is also seen in healthy adults after spending a long time on a task (Newman, O'Connell, & Bellgrove., 2013; Manly et al., 2005) as well as in adults with ADHD (ter Huurne et al., 2013). Hence, a right hemifield bias seems to be related to a suboptimal attentional performance. In our study the rightward bias was associated with a low ability to modulate alpha activity in the left hemisphere and a large cueing effect. One explanation is that a left hemisphere alpha power increase is required to shift attention from right to left, and children have reduced ability in doing so.

Conclusions

In conclusion, we were able to show that the pattern of alpha oscillations modulated by attention is already present in 7 – 10 year old children. However, its relationship with behavioral performance was somewhat opposite as compared to previous findings in adults. Although this seems counterintuitive at first glance, children of this age range exhibit a range of abilities: those with the least maturation of shifting from a rightward to leftward visual bias also exhibit other, possibly less-developed characteristics, namely a larger cueing effect and reduced left alpha MI. The development of attentional networks, and especially the development of attention disengagement may explain why a smaller effect of cued attention allocation may reflect better attentional performance, hence a stronger modulation of alpha activity. In particular our data suggest that children have an enhanced ability to attend to the right; this seems to be explained by alpha oscillations in the left hemisphere not being strong enough to break the attentional focus. Why is this effect only present for the right and not the left hemifield? Given that the ventral network controlled by structures around the right temporal parietal junction (TPJ) is required for exogenously driven attention switches, we speculate that connections from the right TPJ influencing the left hemisphere alpha oscillations remain to mature in children. The fact that alpha modulation is already present at this age opens up the possibility of using lateralized alpha modulation as a tool to mechanistically study clinical attention deficits such as in children with ADHD.

Appendix

Response time distribution

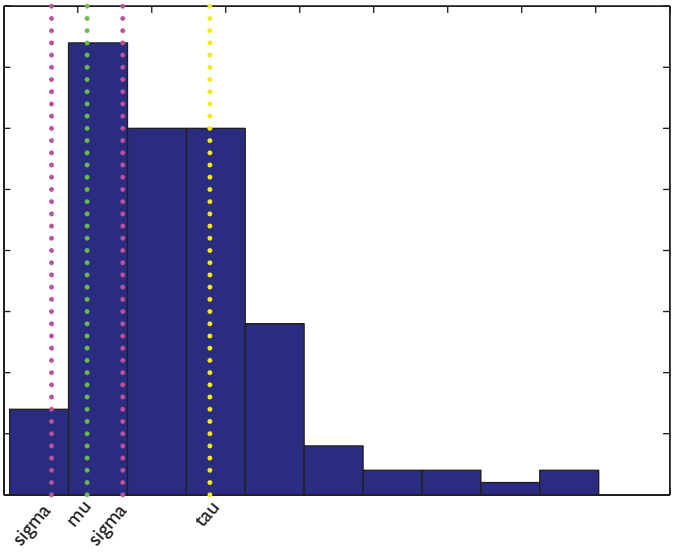


Figure A1. Example of a response time distribution of valid trials.

Target-locked results

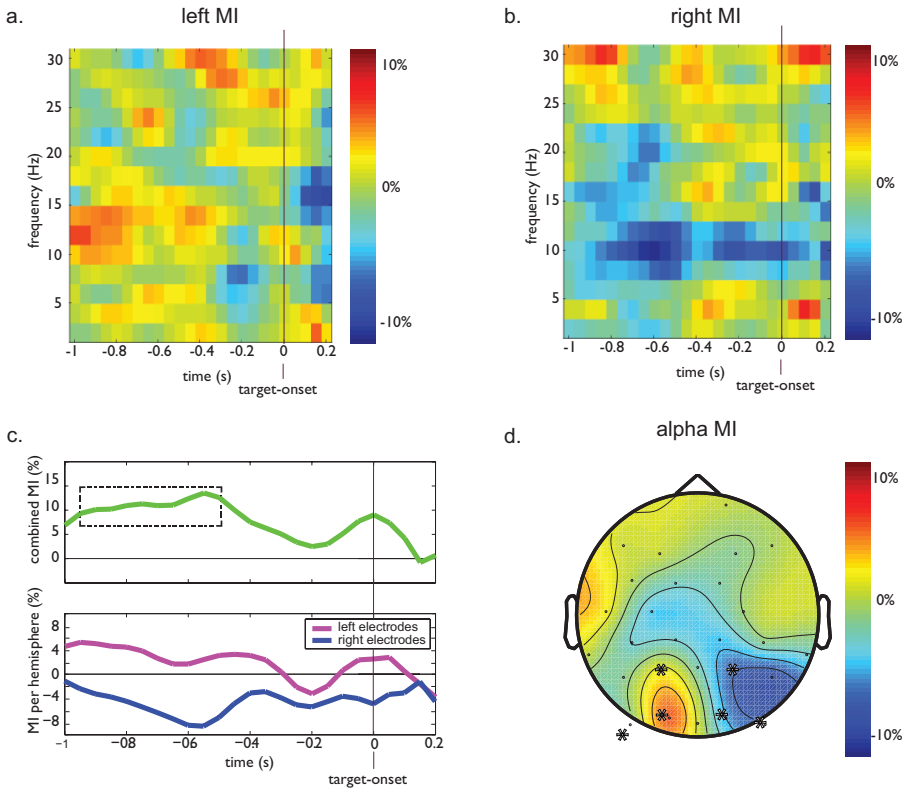
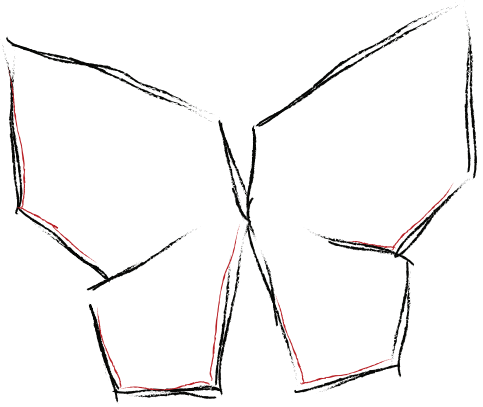


Figure A2. The modulation of alpha band power in response to the spatial cueing, locked to target onset. (*a*). Time-frequency representation of MI of power averaged over children in left occipital and parietal electrodes. The alpha power was stronger for left compared to right cues. The vertical line at zero represents target onset. (*b*). Similar to *a*, for right electrodes. The alpha power was weaker for left compared to right cues. (*c*). Time-course of the combined MI (left electrode MI minus right electrode MI) averaged over children (occipital and parietal electrodes), in the 8-12 Hz alpha band. The dashed square indicates the time cluster for which the MI in left electrodes and right electrodes differed significantly (t = -0.95 – -0.50 s; p = .002) from each other. The vertical line at zero represents target onset. (*d*). Topographic representation of the MI averaged over children, in the alpha band (t = -0.95 – -0.50 s). The alpha power that is clearly lateralized with respect to the spatial cue appears restricted to the posterior electrodes.

Abbreviations: MI: Modulation Index; Hz: Hertz; s: seconds.



Posterior alpha oscillations reflect attentional problems in boys with Attention-Deficit/ Hyperactivity Disorder

Chapter 6 showed that the pattern of alpha oscillations modulated by attentional task performance is already present in 7 – 10 years old typically developing children. The study described in this chapter, aimed to characterize alpha modulations in children with ADHD in relation to their attentional performance. To this end, the posterior alpha activity (8 – 12 Hz) was measured in 30 typically developing children and 30 children with ADHD aged 7 – 10 years, using EEG while they performed a visuospatial covert attention task. We focused the analyses on typically developing boys (N = 9) and boys with ADHD (N = 17). Results showed that, like in **Chapter 6**, alpha activity in typically developing boys was similar to previous results of healthy adults: it decreased in the hemisphere contralateral to the attended hemifield, whereas it relatively increased in the other hemisphere. However, in boys with ADHD this hemispheric lateralization in the alpha band was not obvious (group contrast, p = .018). A robust relation with behavioral performance was lacking in both groups. This study therefore demonstrated that the ability to modulate alpha oscillations in visual regions with the allocation of spatial attention was clearly present in typically developing boys, but not in boys with ADHD. These results open up the possibility to further study the underlying mechanisms of ADHD by examining how differences in the fronto-striatal network might explain different abilities in modulating the alpha band activity.

Based on
Vollebregt, M.A., Zumer, J.M., ter Huurne, N., Buitelaar, J.K., & Jensen, O.
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Introduction

There is increasing evidence that the modulation of brain oscillations in the alpha band (8 – 12 Hz) plays an important role in the allocation of attention. Alpha modulation is thought to gate streams of information through the brain (Klimesch, Sauseng, & Hanslmayr, 2007; Thut & Miniussi, 2009; Snyder & Foxe, 2010) as made specific in the 'alpha inhibition hypothesis' (Jensen & Mazaheri, 2010). The functional role of alpha band activity has particularly been studied in healthy adults using visuospatial covert attention paradigms (Worden, et al., 2000; Sauseng et al., 2005; Kelly et al. 2006; Thut et al., 2006, Händel, Haarmeier, & Jensen, 2011; Bengson, Mangun, & Mazaheri, 2012; ter Huurne et al., 2013). In most electroencephalography (EEG) and magnetoencephalography (MEG) investigations of covert spatial attention, a cue directs attention to the left or right visual hemifield, which allows for investigating alpha power changes in the hemispheres processing the attended and unattended visual hemifields. The key finding is that posterior alpha power increases ipsilateral and decreases contralateral to the attended visual hemifield, respectively inhibiting or facilitating the information flow (Worden et al., 2000; Sauseng et al., 2005; Kelly et al., 2006; Thut et al., 2006, Händel et al., 2011; Bengson et al., 2012; ter Huurne et al., 2013). High alpha power over task-irrelevant regions linked to the processing of the unattended information has proved to be of crucial importance for optimal suppression of distraction (Romei, Gross, & Thut, 2010; Händel et al, 2011).

Typically developing (TD) children have been found to show a similar, adult-like pattern of alpha modulation during covert spatial attention (**Chapter 6**). The behavioral consequences, however, seem to be different than in adults; while previous results in adults showed that alpha modulation was associated with the ability to allocate attention (ter Huurne et al., 2013), this effect did not reproduce in children (see **Chapter 6**).

ADHD is a neurodevelopmental disorder that is characterized by an inappropriate pattern of inattentiveness, hyperactivity and/or impulsivity causing impairment in multiple settings of life (American Psychiatric Association, 2013). A failure to modulate alpha activity might reflect ADHD, given the aforementioned tight links of alpha modulation with attention allocation in healthy adults. Furthermore, adults with ADHD demonstrated a problem in sustaining hemispheric alpha lateralization when cued to the left, resulting in an attentional bias in response times to the right

visual hemifield compared to healthy adults (ter Huurne et al., 2013). Children with ADHD were also found to have a response time bias towards the right visual hemifield in contrast to a leftward bias in TD children (8 – 14 years) (Chan et al., 2009). Younger TD children (5 – 9 years) however, showed a rightward bias (Takio et al., 2013). All in all, it is unclear whether children with ADHD would display deviant lateralized posterior alpha modulation with spatial covert attention similar to adults with ADHD and whether changes in their alpha power would relate to behavioral performance. A study investigating alpha modulation during a cross-modal attention task in children with ADHD showed that significant alpha modulation was absent in these children (Mazaheri et al., 2010). Also, alpha activity was relatively attenuated in ADHD compared to TD children during encoding of a working memory task (Lenartowicz et al., 2014). To date, alpha lateralization by modulating direction of attention was however not studied.

The aim of this study was to investigate alpha modulation in children with ADHD during a covert attentional task, and relate this to TD children and previous observations in adults with ADHD. We hypothesized that children with ADHD would lack a typical alpha modulation pattern and TD children would not. To this end, we compared the modulation of oscillatory brain activity of 7 to 10 year old TD children with children with ADHD as recorded by EEG while performing a visuospatial covert attention task.

7

Materials and methods

Participants

Data were acquired in the context of a clinical trial investigating alpha oscillations in children with and without ADHD (ClinicalTrials.gov identifier NCT01932398). The study was approved by the local Medical Ethics Committee (http://www.cmoregio-a-n.nl/) and conducted in accordance with the Declaration of Helsinki. All parents gave written informed consent; children gave verbal assent.

Children in the age range from 7 to 10 years old were recruited from primary schools in the area of Nijmegen, the Netherlands (TD children) and from referrals to Karakter Child and Adolescent Psychiatry University Centre in Nijmegen, the Netherlands (children with ADHD).

The ADHD DSM-IV rating scale (American Psychiatric Association, 2000 [ADHD-RS-IV]) was filled out for both children with and without ADHD, only reaching the diagnostic cut off point in the first group. It was filled out by parents to rate the current severity of ADHD symptoms. All nine attentional items, six hyperactive items and three impulsive items were rated. This was done using a 4-point Likert scale in which every item is scored as 0 (does never occur), 1 (occurs sometimes), 2 (occurs often) or 3 (occurs very often). For those children that used medication, symptoms were rated when based on time they were withdrawn from medication.

TD children were included if 1) they had never had a psychiatric, neurological, or cardiovascular disease or serious motor or perceptual handicap, 2) they did not score in the clinical range on the ADHD-RS-IV and any subscale of the Child Behavior Checklist (CBCL; Verhulst, van der Ende, & Koot, 1996), both completed by parents, and 3) their estimated IQ was above 80. If an intelligence test had not taken place over the past two years, two subtests (i.e. Vocabulary and Block Design) of the Wechsler Intelligence Scale for Children (WISC-III; Wechsler, 1991; Dutch version: de Kort et al., 2002) were administered to estimate full-scale intelligence. Validity coefficients for the Vocabulary and Block Design scores relative to all subtests scores are .88 for verbal IQ and .83 for performance IQ (Antshel et al., 2007).

Children with ADHD were included if they 1) had received a clinical diagnosis of ADHD according to DSM-IV, 2) scored in the clinical range on the ADHD-RS-IV, completed by parents, and 3) had an estimated IQ above 80. Furthermore, they were allowed to take ADHD-related medication, but had to stop the medication no later than 12 hours prior to the experiment. The presence of clinical behavior on CBCL subscales other than the inattention subscale was discussed with the responsible clinicians to exclude the possibility of a co-morbid diagnosis and verify that ADHD was the primary diagnosis in all cases. Data were collected between April 2012 and December 2014. Parents received reimbursement for travel costs and children received a present.

Initially, 34 TD children and 50 children with ADHD were interested in study participation and were examined on meeting inclusion criteria (*Figure 1*). Two TD children did not meet inclusion criteria and two withdrew from participation. Five ADHD were not enrolled because they did not meet inclusion criteria, 14 withdrew

from participation and one declined due to time constraints of the study. Thus, 60 children participated in this study (TD: N=30; ADHD: N=30). Seven data-sets from TD children were excluded for the following reasons: the child performed below chance-level (<50% correct) (N = 1), there were technical problems (N = 2), the quality of the EEG-data was deficient (N = 1), the child used a different strategy resulting in insufficient correct responses on the invalid trials (for further information, see **Chapter 6**) (N = 3), or withdrew from participation (N = 1). Six data-sets from children with ADHD were excluded for the following reasons: the child performed below chance-level (<50% correct) (N = 1), there were technical problems (N = 2), the quality of the EEG-data was deficient (N = 2), the use of a different strategy resulting in insufficient correct responses on the invalid trials (N = 1), or withdrew from participation (N = 2). Finally, data from twenty-two TD children and twenty-two children with ADHD remained for analysis. However, since we did not counterbalance gender during recruitment, significantly more boys ended up in the ADHD group than in the TD group (TD: 41% boys, ADHD: 77% boys; p = .031, two-tailed Fisher's exact test). More importantly, the ADHD group contained only 5 girls. Previous literature has regularly pointed towards gender differences within ADHD. Gender differences within ADHD have for instance been found in attentional performance (Hasson & Fine, 2012), the functional neuroanatomy of working memory (Valera et al., 2010), and resting state EEG (Dupuy et al., 2013a; Dupuy, Clarke, & Barry, 2013b). Due to this known influence of gender within ADHD and a large influence on the current results (see *The influence of gender*, later in this chapter), we decided to continue analyses with boys only. Therefore, our study will focus on the analysis of 9 TD boys and 17 boys with ADHD. Results including both genders can be found in the appendix of this chapter (*Results for both genders*). Note that the sample of TD children is largely overlapping with the sample of **Chapter 6**.

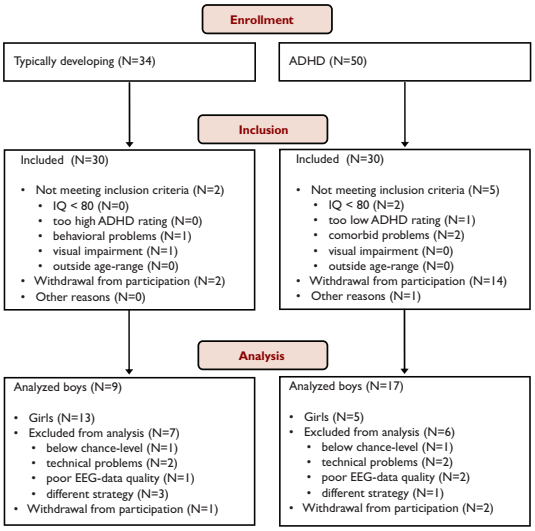


Figure 1. Consolidated Standards of Reporting Trials (CONSORT) flow diagram of participants

Study procedure

The task and data collection procedure were identical to that described in **Chapter 6**. Therefore large parts of the materials and methods section are identical. All measurements were performed at the Donders Centre for Cognitive Neuroimaging, Nijmegen, the Netherlands. Children and their parents visited the institute twice. First, if not available, intelligence was estimated and the Line Bisection Task (Schenkenberg, Bradford, & Ajax, 1980; see *Line Bisection Task* in appendix of this chapter for a description of this task) was performed. Furthermore, the first visit was used to explain and practice the visuospatial covert attention task, subsequently referred to as *the attention task*. This practice session was conducted while tracking the eyes to train the children to keep fixated at the center, but without EEG measurement. During the second visit the attention task was performed while tracking the eyes and recording the EEG. Medicated children with ADHD were not allowed to take their medication on the day of the EEG measurement and had to perform the Line Bisection Task a second time during the second visit, this time off medication. In addition, two resting state EEG sessions, in which the child was instructed to sit quietly for 2 minutes with eyes open and 2 minutes with eyes closed, were recorded during the second visit. We do not report on the resting state data in this dissertation.

The attention task

Like in **Chapter 6**, an adjusted version of Posner's cueing paradigm for spatial orienting of attention was used (Posner, 1980), in which the goal was to save a fish from being eaten by a shark (*Figure 2*). The task was programmed and presented using the software package Presentation (Neurobehavioral Systems, Albany, CA). The task started with a 1-minute introduction video in which a shark recapped the most important instructions. Trials started with a pre-cue period (500 ms) with a shark presented at each side of the screen and a fish presented centrally. The child viewed the screen from a 50 cm distance creating an angle of 5.5 degrees with the innermost edge of the target figures. Note that the most informative part of the target was between the edge (5.5 degrees) and the middle of the target figures (13.1 degrees). The child was instructed to fixate at the fish in the middle of the screen throughout the task. The child was also instructed to sit as quietly as possible. Influences of movement on the eyetracker and EEG recordings were shown to the child in advance to illustrate the importance of sitting still. An attentional cue was presented in a 200 ms interval, in which the fish shifted gaze towards the left or the right shark indicating the side of the upcoming target if validly cued or indicating the opposite side if invalidly cued. In the next period (1000-1500 ms jittered) the child was expected to prepare for the upcoming target, hence this period was referred to as the *preparation period*. Next, the sharks both opened their mouths (100 ms), the target being the shark with the widest mouth. The child had to press the left or right button with the right index or middle finger to indicate the left or right shark, respectively. Correct responses had to be delivered within 1400 ms after target presentation to prevent negative feedback. Depending on the button press, positive or negative feedback was then presented for 500 ms, consisting of a happy fish or a fish bone, respectively. As encouragement a short task-related video with a shark was shown after every 37 trials.

During the first visit, the child practiced 100 trials (40 valid trials and 10 invalid trials per visual hemifield). Hence, the cue predicted the target location in 80% of the trials. During the second visit, the task consisted of 368 trials (138 valid trials and 46 invalid trials per visual hemifield). Hence, the cue predicted the target location in 75% of the trials. The correct prediction of the cue was set higher in the practice session to stimulate the child to use the cue information while learning the task. The left or right cue occurred with equal probability.

Eye tracking

Eye gaze was calibrated using a corneal reflection eye tracker and ClearView software (Tobii 1750, Tobii Technology Sweden), recording both eyes. Following a five point calibration procedure, the eyetracker made it possible to monitor fixation during the pre-cue and preparation period. During the pre-cue period, the cue was presented only when the child fixated on the screen center. If not fixating during the subsequent preparation period, three different types of instruction videos were presented immediately – aborting the trial – depending on the size of the deviation from the middle. It gave instruction to fixate on the eyes of the fish (small deviations), to fixate on the fish (median deviations), or to not look at the sharks (large deviations).

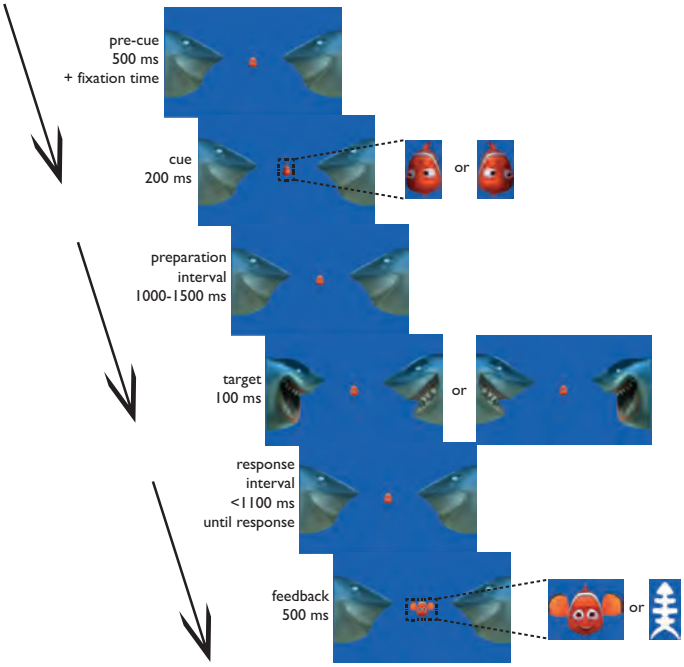


Figure 2. The attention task. After a neutral pre-cue period in which a fish and two sharks were presented on the screen, children were cued to attend to the left or the right visual hemifield while keeping fixation at the centrally presented fish. After a 1000 – 1500 ms preparation interval, both sharks opened their mounts; one more so than the other. Children had to report which shark had the widest opened mouth. In 75% of the trials the widest opened mouth was in the cued visual hemifield (*valid cue trial*), whereas in 25% surprise trials the mouth was widest opened in the other hemifield (*invalid cue trial*). Following a correct response within the response interval, a happy fish was presented. For incorrect responses, the fish was replaced by a fishbone.

EEG recordings

The EEG was recorded from 32 scalp electrodes placed according to the 10-20 system using the Acticap and BrainAmp system (Brain Products GmbH, Munich). The vertex (electrode between Cz and Fz) was used as online reference; offline the data were referenced to the average of all electrodes. Electrode Fpz was used as ground. Electrode impedance was kept below 20 kOhm. The data were sampled at 500 Hz.

Analyses

Data were processed and analyzed using MATLAB 2012a (The MathWorks, Inc., Natrick, MA) and the FieldTrip analysis toolbox (http://fieldtrip.fcdonders.nl). Statistical analyses were also partly conducted employing the SPSS statistical program (SPSS 19.0). When correlation analyses were performed, these were always tested non-parametrically using a Spearman correlation test.

Behavioral performance

Response times (RTs) faster than 100 ms were considered too short to reflect stimulus perception (Luce, 1986), while RTs larger than 4 times the standard deviation of the mean were regarded outliers (Schmiedek et al., 2007). These trials were therefore rejected from behavioral analyses. First, traditional hit-rate and RT analyses – defined as secondary outcome measures in the trial registration – were performed. To this end, percentage correct responses and mean RT and standard deviation were analyzed. However, RTs were expected to be distributed as an exponentially modified Gaussian (ex-Gaussian) distribution, implying that RTs contained a mean (mu) and standard deviation (sigma) of a Gaussian component and a mean (tau) of the exponential component (Lacouture & Cousineau, 2008). Children with ADHD are thought to have slower responses due to a larger tau in particular (Hervey et al., 2006).

Spectral analysis of the EEG data

Data segments showing artifacts such as muscle potentials, and amplifier or electrode noise, were identified using a semiautomatic routine and were excluded from further analyses. An independent component analysis was used to detect and remove component(s) with electrooculographic origin, using a fastica algorithm (Hyvärinen, 1999). The EEG recordings were bandpass filtered at 2 – 30 Hz. Only trials in which the child fixated were used for further analysis. A fast Fourier transformation (FFT),

using a sliding time-window being T = 5 cycles (T = 5/f) long was used to estimate the time-frequency representations of power (2 – 30 Hz in steps of every 2 Hz). The window was advanced in 50 ms increments. Prior to calculating the power using the FFT, the data in each window was multiplied with a Hanning taper. The time-frequency representations of power were calculated per trial and then averaged (Tallon-Baudry and Bertrand, 1999). This method allowed us to have optimal control of time and frequency smoothing. The time interval was cue-locked from -0.25 to 1.5 s with cue-onset at time 0 s. The alpha modulation index (MI) from cue-locked data – our primary outcome measure in the trial registration – was used to investigate whether a task-based modulation could be observed in the alpha band (8 – 12 Hz). The MI was computed by subtracting alpha power of right-cued trials from left-cued trials for each electrode. This subtraction was subsequently normalized by dividing by the mean of these two values:

$$MI = \frac{(alpha_{left\ cued\ trials} - alpha_{right\ cued\ trials})}{\frac{1}{2}\,(alpha_{left\ cued\ trials} + alpha_{right\ cued\ trials})}$$

Since alpha modulation has been observed in occipital and parietal regions in similar tasks (Worden et al., 2000; Thut et al., 2006; **Chapter 6**), we a-priori selected occipital and parietal electrodes (except for the central electrodes Pz and Oz and the most lateral electrodes P7 and P8). The MI was averaged over left (left MI) and right (right MI) hemisphere parietal and occipital electrodes (left: P3, PO9, O1; right: P4, PO10, O2). From these values we constructed a combined MI (left MI minus right MI), which is equivalent to an index based on ipsilateral versus contralateral activity. The MI was computed was based on time-frequency representations of power, allowing us to quantify the MI as a function of time. For parts of the analyses, the MI was subsequently averaged over time.

A cluster based permutation test was performed for each group to identify time clusters for which the left MI differed significantly from right MI (van Ede et al., 2011). This test controls multiple comparisons by identifying significant clusters of time points rather than significant individual time points over the time-interval (-0.2 – 1.5s).

Results

The visuospatial covert attention task performed by the 9 boys without and 17 boys with ADHD is shown in *Figure 2*. The fish in the middle cued the children to attend to the left or the right shark. After a preparation interval (1000-1500 ms), both sharks opened their mouth and the children had to indicate by a button press which of the two sharks opened their mouth the widest. In 75% of the trials, the cued shark opened the mouth the widest, whereas in the remaining 25% trials the uncued shark did so.

Demographic and Clinical Characteristics

The demographic and clinical characteristics are summarized in Table 1. As expected based on the inclusion criteria, there was a significant difference between groups with respect to the ADHD rating (total $t(23.309) = -15.816$, $p < .001$, inattentive: $t(19.681) = -10.895$, $p < .001$, hyperactive/impulsive: $t(21.568) = -16.911$, $p < .001$, independent sample t-tests without the assumption of equal variance) and medication-use ($p = .002$, two-tailed Fisher's exact test). All children were right-handed. There was no difference between groups with respect to age or full-scale IQ. The ADHD group scored higher, and mostly significantly higher, on all problem behavior scales as measured with the CBCL, than the controls (see Table 1).

Task performance

The amount of aborted trials following deviation from fixation was larger in boys with ADHD than boys without (TD: 5 ± 6 trials, ADHD: 16 ± 10 trials; $t(24) = -2.987$, $p = .006$). Trials that were later rejected based on lack of fixation during the preparation interval was also higher in boys with ADHD than boys without (TD: 23 ± 34 trials, ADHD: 52 ± 29 trials; $t(24) = -2.268$, $p = .033$). Trials were also rejected due to artifacts in the EEG signal. After all rejections, the number of valid trials was equal in both groups (TD: 181 ± 33 trials, ADHD: 164 ± 43 trials; $t(24) = 1.037$, $p = .310$) as was the number of invalid trials (TD: 43 ± 8 trials, ADHD: 40 ± 11 trials; $t(24) = 0.620$, $p = .541$). TD boys had significantly more outliers (2 ± 1 trials) than boys with ADHD (0 ± 0 trials), although very small in both groups ($t(24) = 4.457$, $p < .001$), and an equal number of premature responses close to zero ($t(24) = 0.459$, $p = .650$). In sum, a similar amount of trials remained for analyses in both groups.

Table 1. Demographic characteristics

	Typically developing boys (N=9)	Boys with ADHD (N=17)	*p*-value
Age in years, mean (SD)	8.46 (1.38)	9.15 (1.06)	*ns*
(Estimated) full-scale IQ, mean (SD)	121.44 (18.17)	113.53 (14.68)	*ns*
Medication for ADHD, N (%), mean intake in mg (SD)			≤ .01[a]
methylphenidate	0	10 (59), 34.00 (25.68)	
dexamphetamine	0	1 (6), 22.50 (0)	
no medication	9 (100)	6 (35)	
ADHD-RS-IV parent-rated, mean (SD)			
total symptoms	4.56 (2.40)	36.94 (7.17)	≤ .001
inattention symptoms	2.44 (1.67)	19.94 (3.94)	≤ .001
hyperactivity/impulsivity symptoms	2.11 (1.36)	16.88 (5.27)	≤ .001
CBCL (clinical cut-off boys), mean (SD)			
anxious/depressed (≥11)	2.78 (2.54)	4.24 (3.96)	*ns*
withdrawn/depressed (≥6)	1.22 (1.30)	2.59 (2.90)	*ns*
somatic complaints (≥7)	0.89 (1.17)	2.18 (2.46)	*ns*
social problems (≥10)	1.78 (1.56)	4.76 (3.75)	≤ .05
thought problems (≥7)	1.67 (1.73)	3.94 (2.95)	≤ .05
attention problems (≥13)	2.56 (2.24)	10.76 (2.08)	≤ .001
rule breaking behavior (≥7)	0.89 (1.17)	1.59 (1.37)	*ns*
aggressive behavior (≥17)	2.11 (1.96)	9.12 (4.74)	≤ .001
other problems	2.22 (1.56)	5.82 (1.98)	≤ .001

[a] Fisher exact test rather than independent sample *t*-test.

Abbreviations: N: number; *p*-value: probability value; SD: Standard Deviation; IQ: Intelligence Quotient; mg: milligram; ADHD-RS-IV: ADHD DSM-IV Rating Scale; CBCL: Child Behavior Checklist.

Performance measures

Behavioral performance measures between conditions within groups were compared using one-sample t-tests while a comparison between groups was tested using independent sample t-tests. Results can be found in Table 2. TD boys were significantly faster on invalid trials than boys with ADHD (TD: 580 ± 131 ms, ADHD: 686 ± 120 ms, $t(24) = -2.065$, $p = .050$). Within-subject standard deviation of the RTs was larger in boys with ADHD on valid (TD: 127 ± 25 ms, ADHD 176 ± 34 ms, $t(24) = -3.906$, $p = .001$) and invalid trials (TD: 116 ± 38 ms, ADHD: 167 ± 34 ms, $t(24) = -3.497$, $p = .002$). Both groups showed a cueing effect in mean RT (TD: 31 ± 29 ms. $t(8) = -3.1253$, $p = .0141$. ADHD: 50 ± 68 ms, $t(16) = -2.996$, $p = .009$) that did not differ between groups ($t(24) = -0.794$, $p = .433$). When we studied TD children in our previous study (**Chapter 6**), we used ex-Gaussian RT performance measures. We intended to use these measures in the current study as well. However, when comparing groups using ex-Gaussian measures, all above described differences disappeared. When comparing the skewness of the RT distributions, these did not differ between groups ($t(24)=1.457$, $p = .158$). In line with this lack of difference,

but in contrast to our prior expectations, tau did not significantly differ between groups (valid trials; TD: 111 ± 53 ms, ADHD: 115 ± 58 ms. $t(24) = -0.204$, $p = .840$. Invalid trials; TD: 100 ± 53 ms, ADHD: 113 ± 59 ms. $t(24) = -0.575$, $p = .571$). We therefore decided to relate traditional RT performance measures to alpha modulation measures. No significant results differences within or between groups were found on hit-rate. In conclusion, both groups were influenced by the cue, but boys with ADHD varied more in their response times and were slower to respond to invalid trials.

Visual hemifield bias

No systematic group differences with respect to a visual hemifield bias were found. Both groups showed some minor differences between visual hemifields in favor of the right visual hemifield; TD boys showed a larger slowing when having to switch to a left target after being invalidly cued to the right hemifield than in the opposite direction (mean RT when invalidly cued to left: 566 ± 142 ms, mean RT when invalidly cued to right: 595 ± 121 ms, $t(8) = -2.846$, $p = .022$). Boys with ADHD also showed a larger slowing of responses when having to switch to a left target after being invalidly cued to the right hemifield than in the opposite direction (tau RT when invalidly cued to the left: 84 ± 67 ms, tau RT when invalidly cued to the right: 143 ± 75 ms, $t(16) = -3.014$, $p = .008$).

The Line Bisection Task also showed a rightward bias, as indicated by the positive average values in both groups (TD: 2.351 ± 2.263 mm, $t(8) = 3.117$, $p = .014$; ADHD: 4.148 ± 4.006 mm, $t(16) = 4.270$, $p = .001$) without a significant difference between groups ($t(24) = -1.238$, $p = .228$).

Table 2. *Task performance*

Task performance	Typically developing boys (N=9)[a]	Boys with ADHD (N=17)[a]	*p*-value[b]
Hit-rate valid	92.70 ± 11.04	86.02 ± 7.08	*ns*
Hit-rate invalid	87.22 ± 20.03	77.49 ± 21.53	*ns*
Hit-rate cueing	5.48 ± 9.23	8.53 ± 19.30	*ns*
Mean RT valid	550 ± 131	639 ± 148	*ns*
SD RT valid	127 ± 25	176 ± 34	**≤ .001**
Mean RT invalid	580 ± 131	686 ± 120	**≤ .05**
SD RT invalid	116 ± 38	167 ± 34	**≤ .01**
Mean RT cueing	**31 ± 29***	**50 ± 68****	*ns*
SD RT cueing	-10 ± 25	-9 ± 26	*ns*

[a] within group differences between valid and invalid trials are indicated with stars (* $p \leq .05$, ** $p \leq .01$). [b] *p*-value of independent sample t-test

Abbreviations: N: number; *p*-value: probability value; SD: Standard Deviation; RT: Response Time.

Lateralized alpha modulation.

To study hemispheric modulation of oscillations following the cue-initiated allocation of attention, we contrasted the spectral power for left versus right cues for each hemisphere separately and in combination. First we calculated the time-frequency representations of power for left cued minus right cued trials, normalized by their mean and averaged over a-priori chosen left (O1, PO9, P3) and right (O2, PO10, P4) occipital and parietal electrodes. In TD boys, the alpha power decreased in electrodes contralateral to the cue (right electrodes) while it relatively increased in ipsilateral electrodes (left electrodes) (*Figure 3a*). This modulation was absent in ADHD boys (*Figure 3b*). To study the spatial distribution of the effect we next considered the topographical representations. For each group, data were averaged in the interval in which alpha modulation was reported in previous research (ter Huurne et al., 2013) (0.4 – 1.00 s), as well as in the alpha band (8 – 12 Hz). The topographic representations are shown for TD boys (*Figure 3c*) and boys with ADHD (*Figure 3d*). This confirmed that the modulation in the alpha band was strongest over occipital and parietal electrodes in TD boys but was not obvious in boys with ADHD.

To further study the time course we considered the modulation in the alpha band for the left and right hemisphere MI separately (*Figure 4a and 4b; top panel*). By subtracting them we obtained the combined MI (*Figure 4a and b, bottom panel*). A permutation test controlling for multiple comparisons over time verified that left and right MI in the alpha band significantly differed from each other in the interval 0.5 – 0.75 s after cue-onset (p = .012) in TD boys. In boys with ADHD however, no robust power changes were observed in either hemisphere (*Figure 4b, top panel*) or between hemispheres (*Figure 3e, bottom panel*) and no significant time cluster was found.

The average modulation was also considered in the 8 – 12 Hz alpha band in the 0.4 – 1.0 s interval (based on ter Huurne, et al., 2013). Again, occipital and parietal electrodes were used. In this case, a significant difference between left and right was found for both groups (TD: $t(8) = 3.284$, $p = .011$; ADHD: $t(16) = 2.481$, $p = .025$), However, this difference was significantly larger in TD boys than in boys with ADHD ($F(1,24) = 6.407$, $p = .018$) (*Figure 4c*). Such a difference was not found when analyzing the -0.2 – 0.0 s baseline time interval ($F(1,24) = 0.956$, $p = .338$). In sum, these results showed an alpha lateralization pattern in TD boys that was significantly smaller in boys with ADHD.

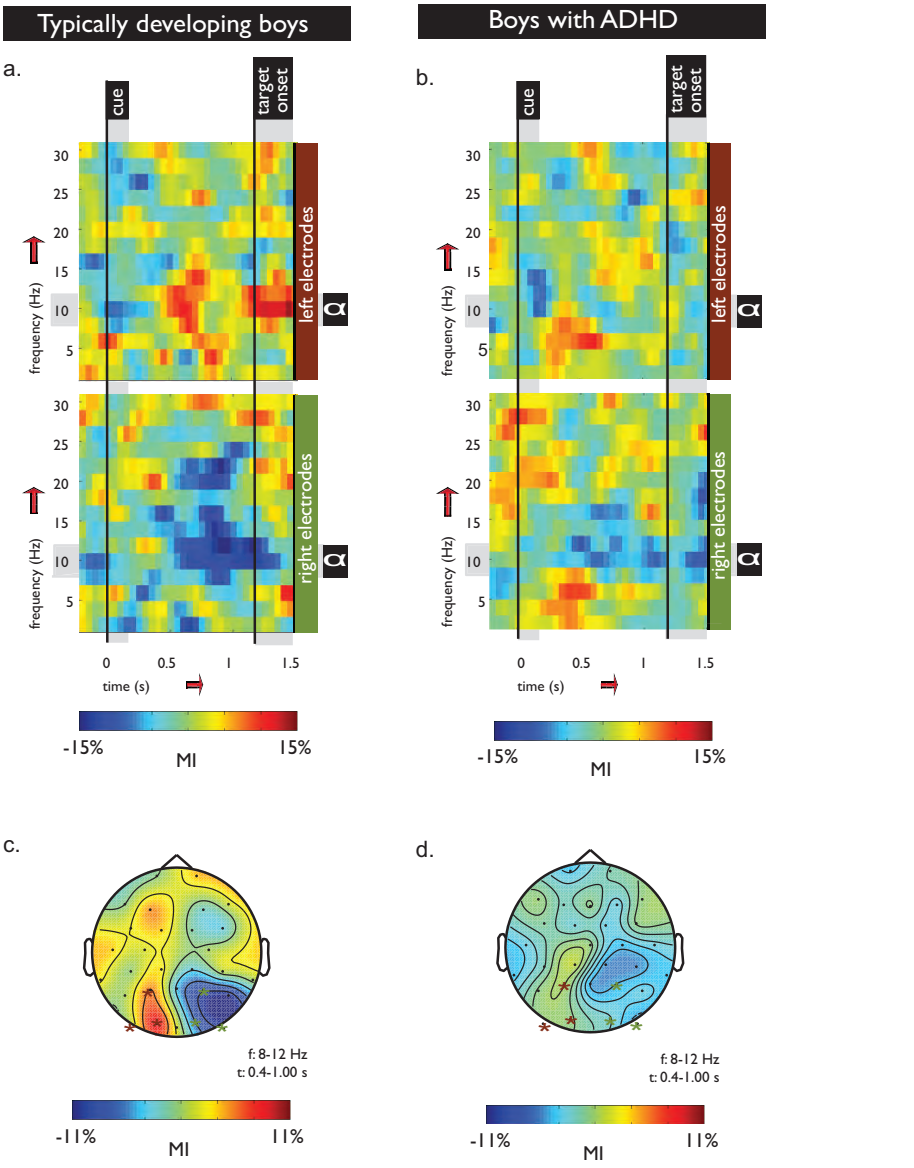


Figure 3. The modulation of alpha band power in response to the spatial cue for TD (left column) and boys with ADHD (right column). (*a*). Time-frequency representation of the normalized MI (left minus right cues) for left (top panels) and right (bottom panels) occipital and parietal electrodes. The MI in the alpha range was postive in left electrodes and negative in right electrodes; i.e. alpha power decreased contralateral to the cue hemifield and increased ipsilaterally. (The line at t = 1.2 s represents first possible target onset and the subsequent grey area the jittered possible onsets of the target presentation). (*b*). The modulation of alpha lateralization was not clearly present in boys with ADHD. (*c&d*). Topographic representation of the MI averaged over children, in the alpha band (t = 0.4 – 1.0 s). The alpha power clearly lateralized over posterior regions in TD boys, but not in boys with ADHD.

Abbreviations: Hz: Hertz; MI: Modulation Index; f: frequency; t: time; s: seconds; Hz: Hertz; α: alpha.

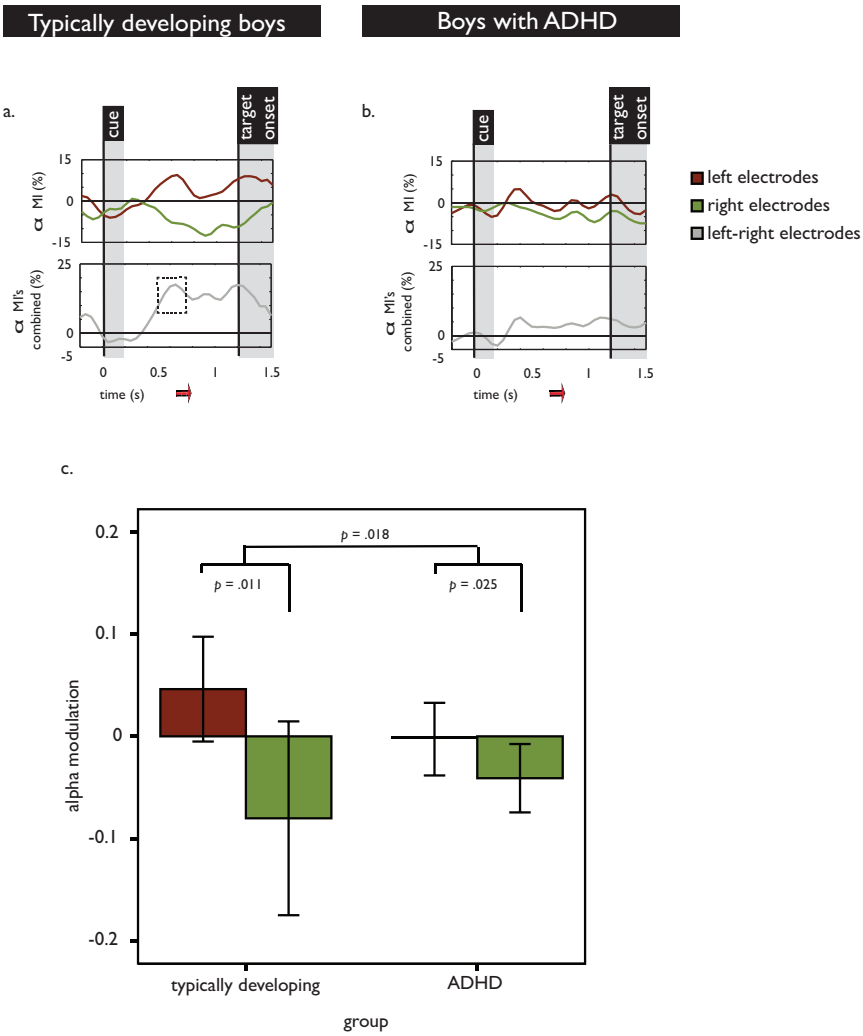


Figure 4. (*a&b*). Time course of the left and right MI, averaged over participants for the 8-12 Hz alpha band occipital and parietal electrodes (top panel). The time course of the combined MI (left electrode MI minus right electrode MI) (bottom pannels). The dashed square indicates the time cluster for which the MI in left electrodes and right electrodes differed significantly from each other in typically developing boys (t = 0.5-0.75; p = .012). *(c)*. Modulation in the alpha band (t = 0.4 – 1.0 s; left and right occipital and parietal electrodes) demonstrating a significant difference between left and right for both groups (TD: $t(8) = 3.284$, p = .011; ADHD: $t(16) = 2.481$, p = .025), This difference was however significantly larger in TD children than in children with ADHD ($F(1,24) = 6.407$, p = .018).

Abbreviations: α MI: alpha Modulation Index; s: seconds.

Lateralized alpha modulation vs behavior

Next, we asked whether the effects of the cue on behavior were related to the alpha MI. First of all, since the amount of aborted trials following deviation from fixation and the later rejected trials based on lack of fixation during the preparation interval was higher in boys with ADHD than boys without, we correlated these values to combined MI. This was done by relating the combined MI, averaged over the alpha frequency band (8 – 12 Hz) and the a-priori selected time points (0.4 – 1.0 s), subsequently combined over electrodes (left minus right) to the ET trial-abortion and ET trial-rejection. This did not result in significant correlations (ET trial-abortion, TD boys: r = .378, p = .316, boys with ADHD: r = -.208, p = .422; ET trial-rejection, TD boys: r = .548, p = .126, boys with ADHD: r = -.214, p = .410). Next, we related combined MI to the cueing effect on hit-rate and mean RT. This also did not result in a significant relationship with the cueing effect on hit-rate (TD boys: r = -.150, p = .700, boys with ADHD: r = -.098, p = .708) or mean RT (TD boys: r = - .000, p = 1.00, boys with ADHD: r = .056, p = .830) for either group. In conclusion, the alpha modulation measures were not related to behavioral performance across individuals in either group.

The influence of gender

The current paper only reported data from boys. This was decided because we only had 5 girls in the ADHD group and gender seemed to have a large influence on the results. We will report the results of the gender comparisons albeit this should be considered tentative due to the low number of girls. An ANOVA with combined alpha MI (averaged over the alpha frequency band [8 – 12 Hz], selected time points (0.4 – 1.00 s), and subsequently combined over electrodes [left minus right]) as dependent variable, group (ADHD vs no ADHD) and gender (boys vs girls) as independent variables, and total IQ – which significantly differed between genders within the ADHD group (boys: 113.529 ± 14.680, girls 98.000 ± 8.746, t(20) = 2.228, p = .038) – as covariate, showed a significant group*gender interaction (F(4,39) = 13.907, p = .001). When including both genders, significant time clusters for which hemispheres significantly differed from each other were found for both children with (t = 0.35 – 0.9 s, p = .004) and without ADHD (t = 0.45 – 1.00 s, p = .004). Furthermore, there was no difference between groups for MI averaged over the alpha frequency band (8 – 12 Hz), selected time points (0.4 – 1.00 s), and either left electrodes (t(42) = 0.581, p = .565), right electrodes (t(42) = -0.123,

p = .903), or left minus right electrodes ($t(42)$ = 0.605, p = .548). The results of both genders are presented in the appendix of this chapter (see *Results for both genders*). However, these are only provided for completeness and to inspire future research. Due to the low number of girls no valid conclusions can be drawn from these results. It would be highly interesting to quantify the gender difference using larger groups in future research.

Discussion

The current study investigated the modulation of alpha band activity in 7 – 10 year old boys with and without ADHD performing a visuospatial covert attention task while EEG was recorded. We found that the alpha power (8 - 12 Hz) in typically developing (TD) boys decreased in the hemisphere contralateral to the attended hemifield, whereas it increased in the other hemisphere, in line with previous findings in adults. This pattern was however not found in boys with ADHD. Specifically, there was a significant difference between groups in the amount of alpha modulation in the difference between hemispheres (lateralization). With respect to behavioral performance, boys with ADHD were slower on invalid trials and more variable in their response times in general than TD boys. However, a clear relationship between the amount of alpha modulation and behavioral responses, such as a cueing benefit in response time or hit-rate, was lacking in both groups.

The absence of alpha modulation in boys with ADHD is in line with previous research in adults showing deviant maintenance of hemispheric alpha lateralization when cued to the left, (ter Huurne et al., 2013). It is also in line with previous research in children showing significant alpha modulation in TD children during a cross modal attention task, but not in children with ADHD (Mazaheri et al., 2010) and children with ADHD showing attenuated alpha activity compared to TD children during encoding of a working memory task (Lenartowicz et al., 2014). Clear evidence for a stronger attentional bias to the right visual hemifield in ADHD than in controls, as found in adults (ter Huurne, et al., 2013), was however lacking. In our previous study (with an overlapping sample), TD children with a large cueing effect, in which lateralized alpha modulation was found to be less pronounced, had a significantly larger bias to the right visual hemifield than children with a small cueing effect (see **Chapter 6**). However, despite less pronounced lateralized alpha modulation in children with ADHD, these children did not have a significantly larger cueing effect

than children without ADHD. Thus, while earlier we established a clear relationship between a cueing benefit and alpha lateralization in healthy adults that was lacking in adults with ADHD. Now we found this relationship also lacking in both children with and without ADHD.

According to the current results, boys with ADHD seem to be unable to modulate alpha activity during covert attentional performance. Why would this be the case? Alpha oscillations are thought to be under top-down control; they can be disrupted by applying transcranial magnetic stimulation to the contralateral frontal eye fields (FEF) (Capotosto et al., 2009; Marshall et al., 2015). The FEF in turn, is thought to be part of the dorsal frontoparietal network for top-down control of visual attention (Corbetta & Shulman, 2002) and under the influence of the dorsolateral prefrontal cortex (Munoz & Schall, 2004). Malfunctions at different levels of the dorsal frontoparietal network could result in deviant top-down control in individual nodes and/or in (functional) connectivity between the nodes. A meta-analysis investigating functional abnormalities in ADHD showed dysfunctions in the right dorsolateral prefrontal cortex, posterior basal ganglia, and parietal areas (Hart et al., 2013). Further evidence showed that saccade-suppression signals in the FEF and superior colliculi are disrupted in ADHD, possibly originating from the prefrontal cortex and/or the basal ganglia by a lack of voluntary control of endogenous fixation (Munoz et al., 2003). Note that significantly more trials were aborted and later rejected based on lack of fixation during the preparation interval in boys with ADHD than boys without, but these rejections did not correlate with alpha modulation. In addition, malfunctioning functional connectivity between frontal attentional control brain systems and the visual cortex in ADHD seems to be supported by a lack of anti-correlation between frontal theta activity and posterior alpha activity on a trial-by-trial basis during a cross-modal attention task in children with ADHD (Mazaheri et al., 2010; Mazaheri et al., 2014).

What may cause these differences within the dorsal frontoparietal network is unclear. It has been acknowledged for decades that modifying the dopaminergic transmission can improve ADHD symptoms (Zametkin & Rapoport, 1987). Dopaminergic neurons seem to play a role in various cognitive processes, amongst others the allocation of attention (Nieloullon, 2002). Although the involvement of dopaminergic dysfunction has long been suspected, the exact nature of its influence on ADHD related behavior remains to be uncovered (Nieloullon, 2002). According to Vaidya & Gordon (2013), there is evidence in ADHD both for low dopamine suggesting a deficit in midbrain-striatal-prefrontal dopamine function and for high dopamine with

higher midbrain dopamine synthesis. These findings do not contradict each other per se; one may act as a compensatory mechanism for the other (Vaidya & Gordon, 2013). Prefrontal dopamine D1 receptors are suggested to contribute to the control that FEF has on the visual cortex (Noudoost & Moore, 2011). Hence, they may have an important role in the dorsal frontoparietal network. The relationship between dopamine and alpha oscillations is – to our knowledge - unknown and could further help us understand the differences within the dorsal frontoparietal network.

The analyses of the current paper focused on boys only. ADHD has been shown to be 2.3 times more common in boys than in girls (Bauermeister et al., 2007). In our sample we only had 5 ADHD girls. Although we did find a significant interaction between group (ADHD vs no ADHD) and gender (boys vs girls) with respect to the difference in alpha modulation between hemispheres, in combination with the low number of girls in the ADHD group (N = 5) this should be considered tentative. In line with previous research on gender differences in ADHD children (Hasson & Fine, 2012; Valera et al., 2010; Dupuy et al., 2013a, Dupuy, Clarke, & Barry, 2013b) and differences in the alpha band in TD children (Clarke et al., 2001a), it would be of great interest to further investigate how the ability to modulate hemispheric alpha lateralization might be different in boys and girls.

Conclusions

In summary, we found that boys with ADHD did not modulate alpha oscillations during a covert attention task like typically developing boys did. A clear relationship between the amount of alpha modulation and behavioral responses was not found in either group. In future studies it would be important to identify the prefrontal and striatal regions that might explain the different ability in modulating the alpha band activity. The top-down control influence of frontal structures and its relation to dopaminergic pathways should also be subject to further investigation. Computational modeling approached and co-registration of EEG and functional Magnetic Resonance Imaging (fMRI) might help to understand the frontoparietal network. Also, genetic information on dopamine could provide more information. Future research should therefore elucidate this different alpha modulation pattern closer by over-recruiting girls with ADHD and more systematically examine gender effects. There is also a need for more systematic studies of the effect of age on alpha modulation by comparing children, adolescents and adults with ADHD cross-sectionally in the same

design and/or by conducting prospective longitudinal studies in children with ADHD. Furthermore, it would be interesting to explore if the aberrant modulation of the alpha band activity is different in different subtypes of ADHD. Such an approach could in the future help diagnosing ADHD subtypes. All in all, this study provides insight into the deviant nature of posterior lateralized alpha modulation, possibly as part of the dorsal frontoparietal network, during covert attention in ADHD. Further understanding the nature of malfunctioning in the dorsal frontoparietal network may eventually help to develop clearly focused treatment of the disorder. Promising with respect to the development of such treatment is the finding that alpha lateralization neurofeedback training has been shown to be superior to sham neurofeedback in healthy adults (Okazaki et al., 2015), demonstrating that these oscillations are trainable.

Appendix

Line Bisection Task

The line-bisection task comprised 17 horizontal black lines of 2-mm width on an off-white sheet of paper (21 x 30 cm). The distance between the lines was 6 mm, except for the distance between the 11th and 12th line, which was 31 mm. The length of the lines ranged from 72 mm to 149 mm, with an average length of 112 mm. They were pseudo randomly positioned so that 5 lines appeared 50 mm from the left margin, 5 lines appeared 50 mm from the right margin and the other 7 lines appeared in the middle of the sheet. The left lateralized lines had lengths of 72, 101, 117, 141, 149 mm, with an average of 114 mm. The right lateralized lines had lengths of 88, 101, 119, 132, 147 mm with an average of 117 mm. The centered lines had lengths of 112, 134, 90, 103, 119, 72, 111 mm with an average of 106 mm. The sheet was laid in front of the child's midline. In a random half of the participants, the sheet was presented upside down, flipping left and right and creating the large distance between the 6th and 7th line. Next, the child was instructed to bisect the line in what he or she thought to be two parts of equal length. This was done with a ballpoint pen. Only one line was presented at a time, the others were covered with two blank off-white sheets of paper. All children performed the task with their right, preferred, hand without any time restrictions.

Results for both genders

Demographic and Clinical Characteristics

The demographic and clinical characteristics of both genders are summarized in Table A1. As expected based on the inclusion criteria, there was a significant difference between groups with respect to the ADHD rating (total: $t(33.053) = -18.649$, $p < .001$, inattentive: $t(34.582) = -16.615$, $p < .001$, hyperactive/impulsive: $t(33.053) = -11.258$, $p < .001$, independent sample t-tests without the assumption of equal variance) and medication-use ($p < .001$, two-tailed Fisher's exact test). There was no difference between groups with respect to age (TD: 8.88 ± 1.18, ADHD: 9.37 ± 1.09; $t(42) = -1.427$, $p = .161$). However, there were significantly more boys in the ADHD group (TD: 41% boys, ADHD: 77% boys; $p = .031$, two-tailed Fisher's exact test) and there was a trend towards a higher full-scale IQ in TD children (TD: 119.45 ± 17.23, ADHD 110.00 ± 14.94; $t(42) = 1.944$, $p = .059$, independent sample *t*-test). Although on average never reaching clinical threshold in either group, most clinical problems as measured with the CBCL occurred significantly more often in the ADHD group (see Table A1 for comparison of all CBCL scales).

Table A1. Demographic characteristics

	Typically developing children (N=22)	Children with ADHD (N=22)	*p*-value
Age in years, mean (sd)	8.88 (1.18)	9.37 (1.09)	*ns*
Gender, N boys (%)	9 (41)	17 (77)	≤ .05[a]
Full-scale IQ, mean (SD)	119.45 (17.23)	110.00 (14.94)	≤ .10
Medication for ADHD, N (%), mean intake in mg (SD)			≤ .001[a]
methylphenidate	0	13 (59), 30.62 (24.17)	
dexamphetamine	0	1 (5), 22.50 (0)	
risperidon	0	1 (5), 0.75 (0)	
no medication	22 (100)	8 (36)	
ADHD-RS-IV parent-rated, mean (SD)			
total symptoms	5.91 (3.84)	37.09 (6.84)	≤ .001
inattention symptoms	2.91 (2.49)	19.91 (4.10)	≤ .001
hyperactivity/impulsivity symptoms	3.00 (2.07)	17.09 (5.49)	≤ .001

Table A1. Continued

	Typically developing children (N=22)	Children with ADHD (N=22)	*p*-value
CBCL (clinical cut-off boys, girls), mean (SD)			
anxious/depressed (≥11, ≥11)	2.09 (2.07)	4.14 (3.56)	≤ .05
withdrawn/depressed (≥6, ≥7)	0.95 (1.13)	2.32 (2.66)	≤ .05
somatic complaints (≥7, ≥7)	1.36 (1.56)	1.86 (2.29)	*ns*
social problems (≥10, ≥9)	1.93 (1.70)	5.00 (3.56)	≤ .001
thought problems (≥7, ≥7)	1.68 (1.70)	4.55 (3.67)	≤ .01
attention problems (≥13, ≥11)	2.36 (2.08)	10.81 (2.24)	≤ .001
rule breaking behavior (≥7, ≥7)	0.64 (0.90)	1.64 (1.47)	≤ .01
aggressive behavior (≥17, ≥16)	2.64 (2.54)	9.55 (4.88)	≤ .001
other problems	2.45 (2.28)	6.23 (2.05)	≤ .001

[a] Fisher exact test rather than independent sample *t*-test

Abbreviations: N: number; *p*-value: probability value; SD: Standard Deviation; IQ: Intelligence Quotient; mg: milligram; ADHD-RS-IV: ADHD DSM-IV Rating Scale; CBCL: Child Behavior Checklist.

Task performance

The amount of aborted trials following deviation from fixation was larger in children with ADHD than children without (TD: 6 ± 6 trials, ADHD: 14 ± 10 trials; $t(34.335) = -3.251$, $p = .003$, equal variances not assumed). Trials that were later rejected based on lack of fixation during the preparation interval was also higher in children with ADHD than children without (TD: 25 ± 26 trials, ADHD: 45 ± 29 trials; $t(42) = -2.499$, $p = .016$). Trials were also rejected due to artifacts in the EEG signal. After all rejections, the number of valid trials was equal in both groups (TD: 180 ± 32 trials, ADHD: 179 ± 53 trials; $t(42) = -0.066$, $p = .948$) as was the amount of invalid trials (TD: 45 ± 8 trials, ADHD: 44 ± 13 trials; $t(42) = -0.208$, $p = .836$). TD children had significantly more outliers (2 ± 1 trials) than children with ADHD (1 ± 1 trials), although very small in both groups ($t(42) = 2.360$, $p = .023$) and an equal amount of premature responses close to zero ($t(42)=-0.830$, $p = .411$). All subsequent task performance measures and the conforming independent sample t-tests between groups are summarized in Table A2.

Performance measures

Behavioral performance measures between conditions within groups were compared using one-sample t-tests while a comparison between groups was tested using independent sample t-tests. Results can be found in Table A2. TD children were better at performing the task than children with ADHD, expressed by a higher hit-rate on valid trials (TD: 92.84 ± 8.32%, ADHD: 85.95 ± 7.25%, $t(42) = 2.930$, $p = .006$) and

invalid trials (TD: 89.32 ± 13.43%, ADHD: 70.46 ± 28.97%, $t(42) = 2.770$, $p = .008$). Also, the hit-rate cueing effect was significant larger in ADHD (15.49 ± 25.64%) than in TD children (3.53 ± 6.65%) ($t(42) = 2.1178$, $p = .040$). Within-subject standard deviation of the response times on valid trials was larger in children with ADHD (TD: 146 ± 34 ms, ADHD 171 ± 36 ms, $t(42) = -2.397$, $p = .021$) as was it on invalid trials (TD: 138 ± 40 ms, ADHD: 173 ± 41 ms, $t(42) = -2.841$, $p = .007$). Both TD children and children with ADHD showed a cueing effect in hit-rate (TD: valid: 92.84 ± 8.32%, invalid: 89.32 ± 13.43%, $t(21)=2.486$, p = 021. ADHD: valid: 85.95 ± 7.25%, invalid: 70.46 ± 28.97%, $t(21) = 2.833$, $p = .010$) and in mean RT (TD: valid: 578 ± 103 ms, invalid: 622 ± 102 ms, $t(21) = -6.146$, $p < .001$. ADHD: valid: 600 ± 165 ms, invalid 667 ± 124 ms, $t(21) = -3.745$, $p = .0012$). When we studied TD children in our previous study (**Chapter 6**), we used ex-Gaussian RT performance measures. We intended to use these measures in the current study as well. However, when comparing groups using ex-Gaussian measures, most above described differences disappeared. Three children were excluded from sigma analyses due to a sigma close to zero. Children with ADHD had a significantly larger sigma on invalid trials ($t(39) = -2.484$, $p = .017$) and there was also a trend towards a significantly larger tau on valid trials in ADHD than in TD children ($t(42) = -1.951$, $p = .058$). A larger tail in the RT distribution in ADHD might still explain the found difference when studying traditional RT performance measures. We therefore decided to relate traditional RT performance measures to alpha modulation measures. In conclusion, both groups were influenced by the cue, but children with ADHD made more errors, had a larger cueing effect, and varied more in their RTs.

Visual hemifield bias

TD children were faster in response to validly cued right sided targets compared to the left (validly left cued mean RT: 585 ± 103 ms, validly right cued mean RT: 571 ± 106 ms, $t(21) = 2.093$, $p = .049$). They also showed a larger slowing when having to switch to a left target after being invalidly cued to the right hemifield than in the opposite direction (mean RT when invalidly cued to left: 608 ± 110 ms, mean RT when invalidly cued to right: 637 ± 98 ms, $t(21) = -3.825$, $p < .001$). Extremely slow responses (tau) happened more often when invalidly cued to the right (tau RT when invalidly cued to left: 91 ± 62 ms, tau RT when invalidly cued to right: 126 ± 66 ms, $t(21) = -3.503$, $p < .002$). Small variation in RT (sigma) happened more often when invalidly cued to the left (sigma RT when invalidly cued to left: 73 ± 33 ms, sigma RT when invalidly cued to right: 57 ± 19 ms, $t(21) = 2.214$, $p < .039$).

In contrast, children with ADHD showed a larger slowing when having to switch to a right target after being invalidly cued to the left hemifield than in the opposite direction when taking into account the ex-Gaussian distribution (mu RT when invalidly cued to left: 568 ± 140 ms, mean RT when invalidly cued to right: 536 ± 132 ms, $t(21) = -2.322$, $p < .030$). However, they also showed more extremely slow responses (tau) when invalidly cued to the right (tau RT when invalidly cued to left: 92 ± 65 ms, tau RT when invalidly cued to right: 136 ± 69 ms, $t(21) = -2.402$, $p < .026$). The Line Bisection Task also showed a rightward bias, as indicated by the positive average values, in both groups (TD: 2.447 ± 3.435 mm, $t(21) = 3.341$, $p = .003$; ADHD: 3.694 ± 3.715 mm, $t(21) = 4.664$, $p < .001$) without a significant difference between groups ($t(42) = -1.155$, $p = .254$).

Table A2. Task performance

Task performance	Typically developing children (N=22)[a]	Children with ADHD (N=22)[a]	*p*-value[b]
Hit-rate valid	92.84 ± 8.32	85.95 ± 7.25	**≤ .01**
Hit-rate invalid	89.32 ± 13.43	70.46 ± 28.97	**≤ .01**
Hit-rate cueing	**3.53 ± 6.65***	**15.49 ± 25.64****	**≤ .05**
Mean RT valid	578 ± 103	600 ± 165	*ns*
Std RT valid	138 ± 40	173 ± 41	**< .05**
Mean RT invalid	622 ± 102	667 ± 124	*ns*
Std RT invalid	138 ± 40	173 ± 41	**≤ .01**
Mean RT cueing	**44 ± 34*****	**68 ± 85*****	*ns*
Std RT cueing	-8 ± 21	1 ± 49	*ns*

[a] within group differences between valid and invalid trials are indicated with stars (* $p \leq .05$, ** $p \leq .01$). [b] *p*-value of independent sample t-test

Abbreviations: N: number; *p*-value: probability value; SD: Standard Deviation; RT: Response Time.

Lateralized alpha modulation

To study hemispheric modulation of oscillations following the cue-initiated allocation of attention, we contrasted the spectral power for left versus right cues for each hemisphere separately and in combination. First we calculated the time-frequency representations of power for left cued minus right cued trials, normalized by their mean and averaged over a-priori chosen left (O1, PO9, P3) and right (O2, PO10, P4) occipital and parietal electrodes. The alpha power decreased in electrodes contralateral to the cue while it relatively increased in ipsilateral electrodes in

both groups (*Figure A1a&b*). To study the spatial distribution of the effect we next considered the topographical representations. For each group, data were averaged in the interval in which alpha modulation was reported in previous research (ter Huurne et al., 2013) (0.4 – 1.00 s), as well as in the alpha band (8 – 12 Hz). The topographic representations are shown for TD children (*Figure A1c*) and children with ADHD (*Figure A1d*). This confirmed that the modulation in the alpha band was strongest over occipital and parietal electrodes in both groups, although less obvious in the left hemisphere of children with ADHD.

To further study the time course we considered the modulation in the alpha band for the left and right hemisphere MI separately (*Figure A2a and A2b; top panel*). By subtracting them we obtained the combined MI (*Figure A2a and b, bottom panel*). A permutation test controlling for multiple comparisons over time verified that left and right MI in the alpha band significantly differed from each other and that this difference was most pronounced in the interval 0.45 – 1.00s after cue-onset (p = .004) in TD children and was also significant in children with ADHD in the interval 0.35 – 0.9s after cue-onset (p = .004).

The average modulation was also considered in the 8 – 12 Hz alpha band in the 0.4 – 1.0 s interval (based on ter Huurne, et al., 2013). Again, occipital and parietal electrodes were used. In this case, a significant difference between left and right was found for groups (TD: $t(21) = 4.210$, $p < .001$; ADHD: $t(21)$ 3.686, $p = .001$), This difference was not larger in TD children than in children with ADHD ($F(1,42) = 0.367$, $p = .548$) (*Figure A2c*). In sum, these results showed an alpha lateralization pattern in TD children did not significantly differ from children with ADHD.

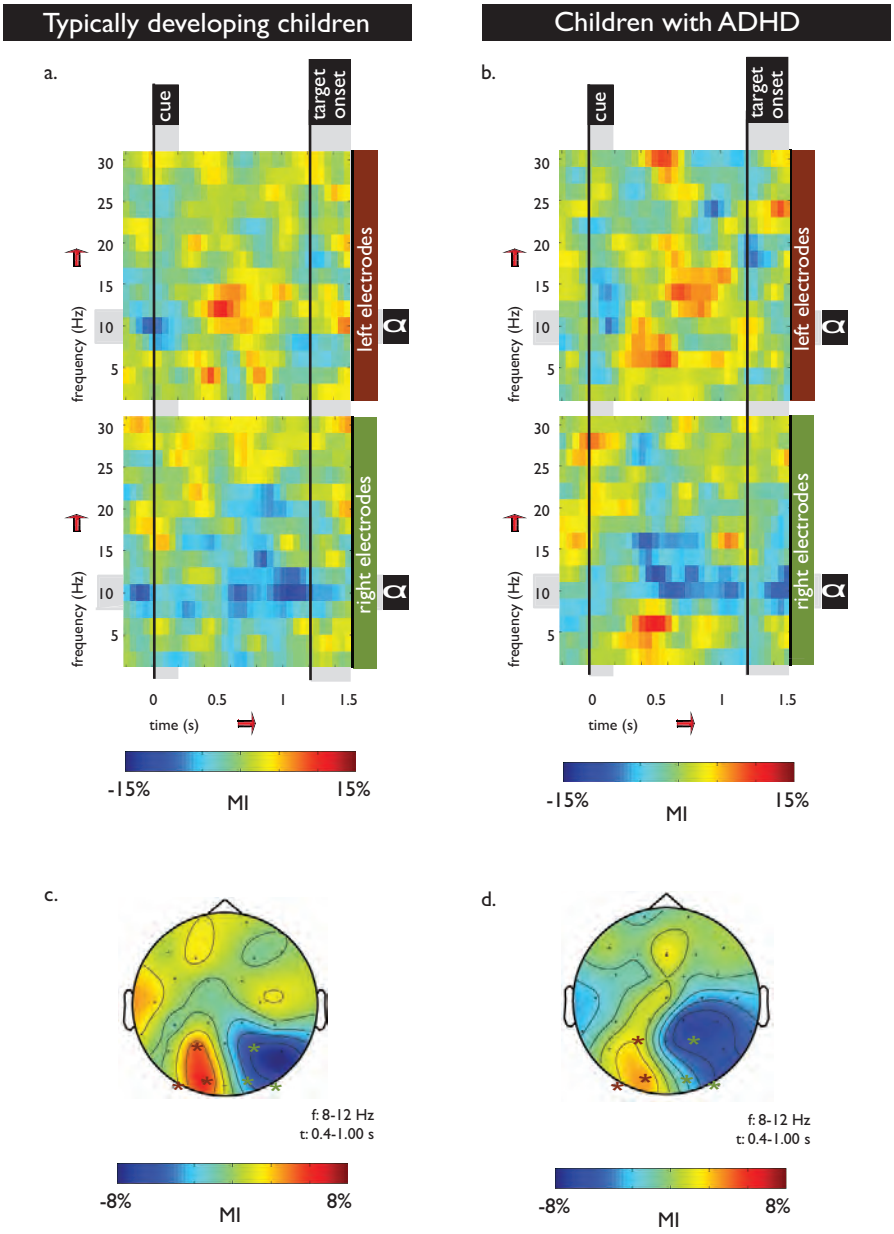


Figure A1. The modulation of alpha band power in response to the spatial cue for TD children (left column) and children with ADHD (right column). (*a&b*). Time-frequency representation of the normalized MI (left minus right cues) for left (top panels) and right (bottom panels) occipital and parietal electrodes. The MI in the alpha range was positive in left electrodes and negative in right electrodes; i.e. alpha power decreased contralateral to the cue hemifield and increased ipsilaterally. The line at t = 1.2 s represents first possible target onset and the subsequent grey area the jittered possible onsets of the target presentation. (*c&d*). Topographic representation of the MI averaged over children, in the alpha band (t = 0.4 – 1.0 s). The alpha power clearly lateralized over posterior regions in TD children, but less obvious in (the left hemisphere of) children with ADHD.

Abbreviations: Hz: Hertz; MI: Modulation Index; f: frequency; t: time; s: seconds; Hz: Hertz; α: alpha.

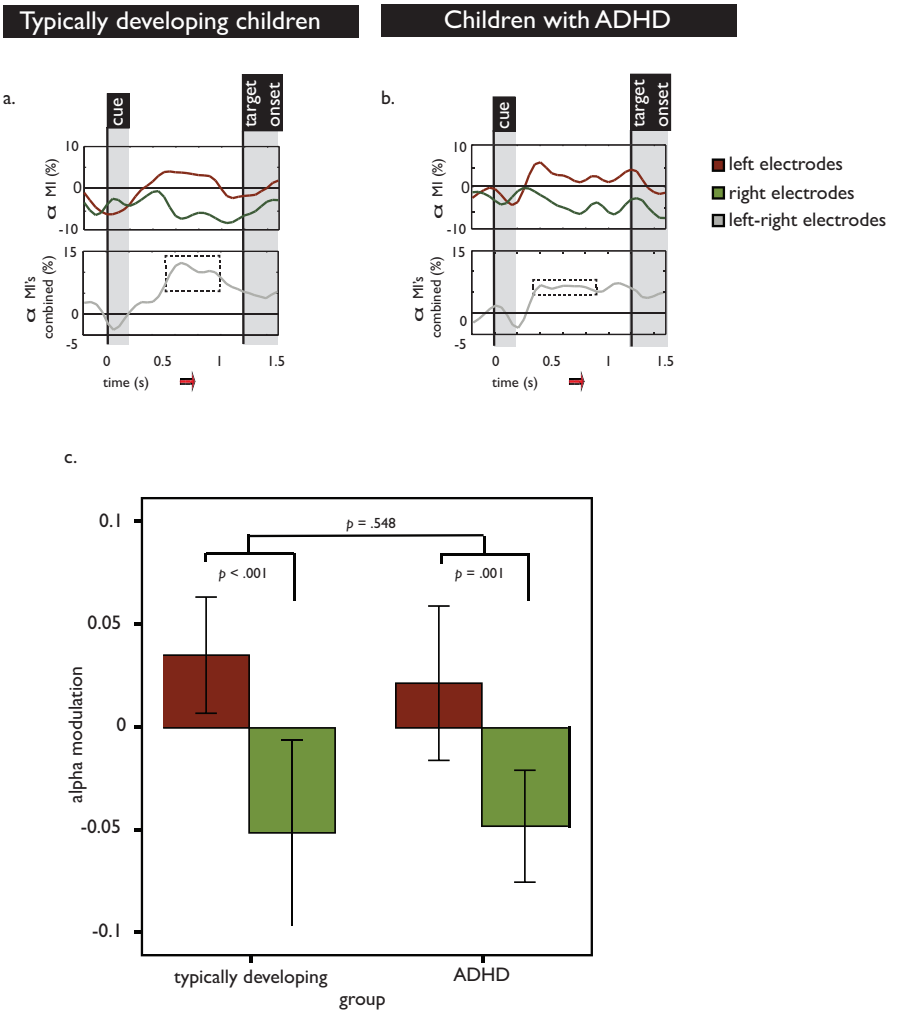
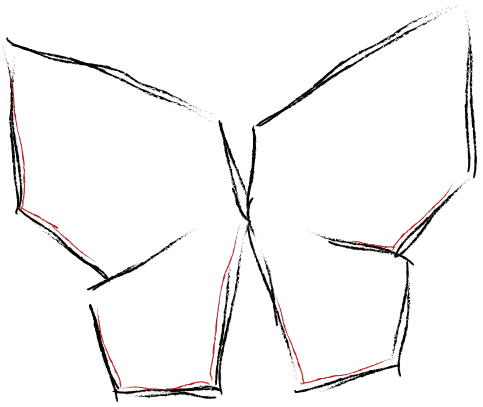


Figure A2. (*a&b*) Time course of the left and right MI, averaged over participants for the 8-12 Hz alpha band occipital and parietal electrodes (top panel). The time course of the combined MI (left electrode MI minus right electrode MI) (bottom pannels). The dashed square indicates the time cluster for which the MI in left electrodes and right electrodes differed significantly from each other in typically developing children (t = 0.45-1.00; p = .004) and children with ADHD (t = 0.45-1.00; p = .004). (*c*) Modulation in the alpha band (t = 0.4 – 1.0 s; left and right occipital and parietal electrodes) demonstrating a significant difference between left and right for both groups (TD: $t(21) = 4.210$, $p < .001$; ADHD: $t(21)$ 3.686, p = .001), This difference was not larger in TD children than in children with ADHD ($F(1, 42) = 0.367$, p = .548).

Abbreviations: α MI: alpha Modulation Index; s: seconds.

Lateralized alpha modulation vs behavior

Next, we asked whether the effects of the cue on behavior were related to the alpha MI. First of all, since the amount of aborted trials following deviation from fixation and the later rejected trials based on lack of fixation during the preparation interval was higher in children with ADHD than children without, we correlated these values to combined MI. This was done by relating the combined MI, averaged over the alpha frequency band (8 – 12 Hz) and the a-priori selected time points (0.4 – 1.0 s), subsequently combined over electrodes (left minus right) to the ET trial-abortion and ET trial-rejection. This did not result in significant correlations (ET trial-abortion, TD children: r = -.233, p = .296, children with ADHD: r = -.102, p = .650; ET trial-rejection, TD boys: r = -.164, p = .466, boys with ADHD: r = -.114, p = .813). Next, we related combined MI to the cueing effect on hit-rate and mean RT. This also did not result in a significant relationship with the cueing effect on hit-rate (TD children: r =.059, p = .793, children with ADHD: r = -.399, p = .066) or mean RT (TD children: r = - .019, p = .934, children with ADHD: r = .117, p = .604) for either group. In conclusion, the alpha modulation measures were not related to behavioral performance across individuals in either group.



Overview of the results and general discussion

In this doctoral dissertation, EEG-neurofeedback was investigated, reviewed, and discussed as a potential treatment for children with ADHD. Furthermore, brain oscillations of children with and without ADHD were investigated. In this chapter I will evaluate the progress that was made based on the results; I will summarize and discuss the results, list all key observations and conclusions derived from the previous six chapters. Finally I will discuss clinical implications and future directions.

Summary

In **Chapter 2**, resting-state EEG measurements in relation to the core-behavioral symptoms of ADHD and the performance on neurocognitive tasks were explored and analyzed using the measurement before treatment-onset of the first study sample (see *Aims and outline of the dissertation* of **Chapter 1** for a description of the study samples). More specifically, we assessed whether the theta/beta power ratio and relative theta power correlated with behavioral functioning in children with ADHD as expected from previous work. In addition, the influence of the individual alpha peak frequency was studied. To this end, EEG data, investigator-scored ADHD IV Rating Scales, and neurocognitive data were analyzed. The results of this study confirmed that the theta/beta power ratio and theta power indeed correlated with behavioral symptoms in children with ADHD. This was not the case for neurocognitive functioning. The individually determined alpha-band was low in 21% of the children. Foremost, the relationship between theta power and total symptom score after controlling for individual alpha peak frequency changed from non-significant to a strong significant correlation underlining the relevance of taking the individual alpha peak frequency into account.

In **Chapter 3** and **Chapter 4**, the efficacy and safety of EEG-neurofeedback in children with ADHD was studied. A stratified, semi-randomized double-blind placebo-controlled treatment design was used to investigate the efficacy of EEG-neurofeedback in the first study sample (see *Aims and outline of the dissertation* of **Chapter 1** for a description of the study samples). Children with a DSM-IV-TR diagnosis of ADHD were randomly allocated to EEG-neurofeedback or placebo-neurofeedback treatment for 30 sessions, twice a week. The children were stratified by age, electrophysiological state of arousal, and medication use. Everyone involved in the study, except the neurofeedback therapist and the principal investigator, was blinded to treatment assignment. The primary outcome described in **Chapter 3** was the severity of ADHD core-symptoms on the ADHD Rating Scale IV, scored at baseline, during treatment, and at study end. Clinical improvement as measured by the Clinical Global Impressions-Improvement (CGI-I) scale was a secondary outcome. No significant treatment effect on any of the behavioral outcome measures was found. In **Chapter 4**, we focused on the changes in neurocognitive performance (neurocognitive tests measuring executive functioning, attention, reward-related processes, and timing) before and after treatment. No significant treatment effect

on any of the neurocognitive outcome measures was found either. Furthermore, a systematic review of the current literature also did not find any systematic beneficial effect of EEG-neurofeedback compared to control conditions on neurocognitive functioning (**Chapter 4**). Based on these results, EEG-neurofeedback was not superior to placebo-neurofeedback in improving ADHD symptoms or neurocognitive functioning in children with ADHD. However, **Chapter 5** emphasized that absence of evidence does not equate with evidence of absence, and discussed how future research might overcome methodological limitations of the current studies. Furthermore, **Chapter 5** provided suggestions for the development of improved forms of neurofeedback.

Next, the aim of the study described in **Chapter 6** was to characterize alpha modulations in children in relation to attentional performance. Typically developing children from the second study sample (see *Aims and outline of the dissertation* of **Chapter 1** for a description of the study samples) were tested to investigate lateralized alpha modulation using EEG during covert attentional task performance in this young target group (7 – 10 years old). We found that – like in adults – the alpha activity decreased in the hemisphere contralateral to the attended hemifield, whereas it relatively increased in the other hemisphere. In addition, we found that – in contrast to adults – the degree of lateralized alpha modulation predicted performance on the attention task by negatively predicting the response time on invalid trials. Of note, children who were behaviorally less influenced by spatial cueing, also were children with a significantly stronger alpha lateralization in the left hemisphere than children who were influenced more by spatial cueing. In addition, a bias to the right visual field that is commonly observed in children, was significantly smaller or absent in the children influenced least by spatial cueing. Among all children, the magnitude of this visual field bias was positively related to the ability to modulate alpha activity. In conclusion, we showed that the pattern of alpha oscillations modulated by attention is already present in 7 – 10 year old typically developing children. Although a similar pattern is observed in adults, the consequences for behavior are different.

Finally, in **Chapter 7** we aimed to characterize alpha modulations in children with ADHD in relation to their attentional performance. Typically developing boys and boys with ADHD from the second study sample (see *Aims and outline of the dissertation* of **Chapter 1** for a description of the study samples) were tested. The rationale to study boys is further explained in the subsequent *General discussion*.

Like in **Chapter 6**, lateralized alpha modulation using EEG during covert attentional task performance was measured. We demonstrated that the ability to modulate alpha oscillations in visual regions with the allocation of spatial attention was clearly present in typically developing boys, but not in boys with ADHD. Alpha activity in typically developing boys was similar to previous results of healthy adults (and of children from the largely overlapping sample of **Chapter 6**): it decreased in the hemisphere contralateral to the attended hemifield, whereas it relatively increased in the other hemisphere. However, this hemispheric lateralization in the alpha band was diminished in boys with ADHD compared to typically developing children. A robust relation with behavioral performance was lacking in both groups. In this chapter, we therefore showed that the pattern of alpha oscillations modulated by attention that was already present in 7 – 10 year old typically developing boys, but was not visible in boys with ADHD.

General discussion

The aims of this dissertation were to answer four research questions, as defined in the introduction. In this section, I will discuss those in the light of the findings of the empirical chapters (**Chapter 2-7**).

Answers to the research questions

1. Is there a relationship between the theta/beta power ratio and theta power, and behavioral functioning using a broad range of behavioral measures? Are these relationships influenced by the individual alpha peak frequency?

Although a lot of research has been conducted on resting-state oscillations in ADHD, inconsistent findings such as opposite correlations (both negative and positive) between different frequency bands and symptom ratings (see **Chapter 1**, *Resting state neuronal oscillations in ADHD*), complicate the interpretation of these studies. The study described in **Chapter 2** aimed to shed light on these inconsistencies. Different reasons may underlie inconsistencies in findings. First, although EEG may be regarded as a more objective measure than subjective ratings of core-behavioral

symptoms, behavioral measurements are based on much longer time periods than EEG recordings. While symptoms are assessed by reviewing the whole developmental history, EEG-recordings are snapshots, more vulnerable to temporary (contextual) changes during measurement (Kendler & Neale, 2010). These influences may be complemented by the multifactorial causation of ADHD leading to a heterogeneous profile of psychopathology, neurocognitive deficits, and abnormalities in the structure and function of the brain (Faraone et al., 2015). Furthermore, methodological differences between studies may underlie inconsistencies in findings. Examples of such differences are types of recording (eyes open vs eyes closed, used EEG systems, absolute vs relative power), diversity in demographics (age, gender, and ADHD subtypes [i.e., ADHD presentations]) and in measures (behavioral rating scales and neurocognitive tasks), and ways of dealing with the multiple comparisons problem. Although the study described in **Chapter 2** was also subject to the listed reasons for inconsistent findings in previous research, this study focused on one of the possible reasons of inconsistent findings within the ADHD-literature. More specifically, we scrutinized the most consistent finding in the ADHD-literature; elevated absolute theta power (Arns, 2012), which is also incorporated in the theta/beta power ratio, seen in a substantial subgroup of ADHD patients (for meta-analysis, see Arns, Conners, & Kraemer, 2013). Our study was driven by the hypothesis that alpha peaks at a lower frequency than typically developing age-averages in a subgroup of children with ADHD, thereby influencing the estimation of theta activity. We a-priori chose to study 'individualized alpha peak frequencies' and 'non-individualized (i.e. fixed) relative theta power' (for details, see **Chapter 2**). We specifically hypothesized that 1) theta power, and the theta/beta power ratio would be positively related to core-behavioral symptoms of ADHD and impaired neurocognitive functioning within the ADHD group, and that 2) low individual alpha peak frequencies would influence these relationships by showing an overlap between the individualized alpha-band and the fixed theta-band of 4 – 8 Hz, thereby falsely overestimating theta power.

Results were in line with the first hypothesis with respect to the core-behavioral symptoms; a positive relationship was found between relative theta power and hyperactive/impulsive symptoms. Further, a positive relationship was found between the theta/beta power ratio and the total symptom score and hyperactive/impulsive symptom sub-score. The second part of the first hypothesis was rejected; no relationships were found with neurocognitive functioning.

The second hypothesis was confirmed; twenty-one percent of the children in our study showed an overlap between the individualized alpha-band and the fixed theta-band; controlling for the individual alpha peak frequency strengthened the first hypothesis.

Although the second hypothesis was confirmed, previous research may have yielded a different expected direction. Lansbergen and colleagues (2011a) demonstrated that a difference between ADHD and typically developing children in theta/beta power ratio based on fixed frequency bands was *lacking* when using individualized frequency bands anchored to the individual alpha peak frequencies. We, on the other hand, observed *strengthening* of the relationships with core-behavioral symptoms. This difference can be explained by a difference in approach. The current study aimed to investigate the influence of individualized alpha band power on the *conventional* 4 – 8 Hz theta-band, rather than individualizing *all* frequency bands like Lansbergen and colleagues did. By using such a fixed theta-band comparable to the majority of earlier studies (Arns et al., 2013), we were able to show that controlling for the individually based alpha peak frequency enhanced the conventional theta and theta/beta power ratio relationship with the core symptoms of ADHD (for further discussion on this topic, see **Chapter 2**). The fact that the first hypothesis was not confirmed with respect to neurocognitive functioning, may be due to similar reasons to those that yielded inconsistent findings between studies, i.e. multifunctional causation of the disease, temporary changes during (both EEG and neurocognitive) measurements, and methodological aspects of the study.

In summary, results of the study described in Chapter 2 showed a relationship between the conventional theta/beta power ratio and theta power, and behavioral functioning. Furthermore, results suggest that the frequency at which alpha is peaking in individuals may influence previously studied relationships between electrophysiological and behavioral measures.

Individual differences in alpha peak frequency may account for part of the inconsistencies found in results from previous studies. Because controlling for the individual alpha peak frequency changed the relationship between theta power and total symptom score from non-significant to a strong significant correlation, this suggests that resting-state theta power is *actually* associated with ADHD

core-symptoms. Theta power has been related to working memory performance (Jensen & Tesche, 2002; see *Electrophysiological frequency bands* in **Chapter 1**), a neurocognitive domain that also has been shown to be affected in children with ADHD (Willcut et al., 2005). Furthermore, in infants and preschool children, theta activity has been related to behavioral states with substantial attentional and emotional load (Orekhova et al., 2006). Studying theta-oscillations during attentional or working memory performance would therefore provide valuable insights. In addition, the fact that a subgroup of children with ADHD shows a low individual alpha peak frequency suggests that – following the alpha inhibition hypothesis – the process of allowance and stopping of information transfer is slower in these children (Grandy et al., 2013). Alpha oscillations during task performance in boys with ADHD were further explored in **Chapter 7** (see also the discussion of the last research question).

2. *Does current daily practice EEG-neurofeedback have a positive effect on symptomatic and neurocognitive functioning in children with ADHD?*

This dissertation described the behavioral (**Chapter 3**) and neurocognitive (**Chapter 4**) outcome of our semi-randomized double-blind placebo-controlled treatment study, as well as a systematic review of the current literature on neurocognitive outcome measures of EEG-neurofeedback (**Chapter 4**). At the time this study was set up no placebo-controlled studies investigating the efficacy of EEG-neurofeedback in ADHD were performed yet. Furthermore, a discussion on the current state of affairs with respect to EEG-neurofeedback both as treatment and as research topic was described (**Chapter 5**).

Summarizing the results of our study, we could not show superior efficacy compared to the placebo condition on core-behavioral symptoms, neurocognitive, and global clinical functioning in children with ADHD investigating EEG-neurofeedback delivered as "care as usual". Fortunately, no adverse (side)-effects were found either, indicating EEG-neurofeedback to be a safe intervention.

EEG-neurofeedback has the purpose to improve brain functioning (Hammond et al., 2011). Via improved brain functioning, behavioral improvement should be established. However, evidence of improvement in neural regulation, suggesting improved brain functioning, has sparsely been investigated. Therefore it is often not clear at what

level a treatment failed. In our study, we investigated the trained EEG-targets for children in the EEG-neurofeedback group across sessions and did not find support for better neural regulation with time spent on the treatment (see **Chapter 4**). Interestingly, even when analyzing the clinical responders only, no improvement in neural regulation was found. These results are not in line with the assumption that improved neural regulation is mediating improved behavior.

Despite strong research interest in EEG-neurofeedback (see *The history of EEG-neurofeedback* in **Chapter 1**), the question whether EEG-neurofeedback is an effective treatment for ADHD is still unanswered. Based on a meta-analysis in 2009, EEG-neurofeedback was regarded efficacious and specific, with large effect sizes for inattention (ES [Hedges' D] = 1.02) and impulsivity (ES = 0.94) and a medium effect size for hyperactivity (ES = 0.71) (Arns et al., 2009). However, as Holtmann et al. (2014) pointed out in their review, before such a claim can be validly made there is strong need for more evidence from methodologically sound and sensitive study-designs incorporating proper blinding. Importance of proper blinding became apparent from the meta-analyses by Sonuga-Barke et al. (2013), including the pilot-study preceding the study described in **Chapter 3-4** of this dissertation (Lansbergen et al., 2011b). While a significant treatment effect on the total ADHD symptom score was found for proximal, often non-blinded, raters (SMD = 0.59 [0.31, 0.87], p = .001), the effect size for probably blinded assessments was small (SMD = 0.29 [-0.02, 0.61], p = .07). An update of this meta-analysis, increasing the analysis with 84 participants (including the data from **Chapter 3)**, again showed no significant effect on the overall ADHD score for probably blinded assessments (SMD = 0.18 [-0.07, 0.42], p = .15). However, this meta-analysis also investigated the different symptom categories and did find a significant medium-sized effect on the probably blinded assessment of inattention (SMD = 0.30 [0.03, 0.58], p = .03), but not for hyperactivity/impulsivity (SMD = 0.14 [-0.10, 0.39], p = .26) (Michoulaud-Franchi et al., 2014). They also investigated the size of the random error, which was clearly higher for probably blinded assessments. Note that probably blinded measures in this meta-analysis were from teachers, thereby stressing the importance of designs with blinded measures of raters that do not enhance the random error. This would likely be a blinded proximal rater, i.e. a blinded parent or investigator. A way to easily include such blinded measures is by double-blind assignment to active treatment or placebo treatment. Until now, the majority of studies investigating EEG-neurofeedback did not include a placebo condition, partly due to difficulties to provide optimal EEG-neurofeedback if the therapist is

blind. Given the finding that our placebo condition showed an improvement that was similar to the EEG-neurofeedback condition, results of the studies lacking a placebo condition do not allow for conclusive evidence of the nature of improvement. The inclusion of a placebo condition enables the allocation of positive findings to the working element of the treatment, creates equal expectancy between groups, and can easily include blinded measures in the evaluation of the treatment. However, a placebo-condition may also have drawbacks that would be circumvented in other study-designs (for further discussion on this topic, see **Chapter 5**). Although both children and their parents, and the investigators were blind to treatment assignment in our study, the EEG-neurofeedback therapists were not post pilot-phase. The Collaborative Neurofeedback Group has proposed a promising multisite study by creating a design in which real-time noise is superimposed on the placebo data creating the illusion of real time EEG recordings, thereby also enabling a blinded therapist (The Collaborative Neurofeedback Group, 2013).

In addition to the ongoing study from The Collaborative Neurofeedback Group in which current EEG-neurofeedback is investigated, development of new (EEG-) neurofeedback methods should continue. To date, EEG-neurofeedback studies are empirically driven. Empirical strategies to improve EEG-neurofeedback can generate findings to further improve EEG-neurofeedback protocols, but also to provide clues on the underlying mechanisms. In turn, the field of cognitive neuroscience is progressing so fast that new evidence on the relationship between neuronal oscillations and cognitive processes within this field, can further improve EEG-neurofeedback protocols. Horschig and colleagues (2014) proposed that neuroscientific knowledge about neuronal oscillations could help to develop hypothesis-driven methods to augment cognition by optimizing cortical oscillations. Hypothesis-driven neurofeedback would build on the principles of hypothesis-driven brain-computer interfacing (Jensen et al., 2011). Such an approach forces researchers to focus on the most robust task-dependent modulations of brain signals. Only with the use of robust measures, it is possible to establish hypotheses a-priori for applying EEG-neurofeedback. Horschig and colleagues proposed to train lateralized alpha modulation during visual spatial attention task performance or frontal theta activity during working memory performance. Note that the specific task that is used and the oscillations that are trained should reflect the underlying cognitive mechanism that is trained. In that way, neuronal oscillations that are known to deviate from controls during task performance can be trained very specifically.

Although a hypothesis-driven approach may have a more straightforward rationale than the conventional empirical approach, the question remains whether the normalization of these oscillations via feedback would lead to an actual improvement of behavior. To date, despite a difference on group-level, a causal link between for instance lateralized alpha modulation and the core-symptoms of ADHD remains to be established (see **Chapter 7**). Hence, an improvement of lateralized alpha modulation does not readily imply an improvement on behavioral level. Transfer trials, discussed in **Chapter 5**, aim to narrow the gap between task setting and daily life. Further research is needed to investigate the potential of hypothesis-driven neurofeedback.

All in all, current research does not provide evidence for a positive effect of current daily practice EEG-neurofeedback on symptomatic and neurocognitive functioning in children with ADHD that is superior to placebo. However, both the treatment and study-protocols require improvements before completely rejecting the potential positive effect of neurofeedback.

3. *How do lateralized alpha modulations observed in children relate to previous observations in adults?*

To be able to investigate children with ADHD with respect to lateralized alpha modulation (discussed in answer to the next research question), it was important to first verify that typically developing children were able to perform the task and showed similar oscillatory patterns to adults. Typically, adults have been shown to display posterior alpha power increase ipsilateral and alpha power decrease contralateral to the attended visual hemifield (Worden et al., 2000; Sauseng et al., 2005; Kelly et al., 2006; Thut et al., 2006; Händel, Haarmeier, & Jensen, 2011; Bengson, Mangun, & Mazaheri, 2012; ter Huurne et al., 2013). With this often-replicated finding, evidence is building up for a functionally inhibiting role of alpha oscillations in adults. However, since – to our knowledge – children were never subject to similar study protocols at the time of the study, we investigated the modulation of oscillatory brain activity as recorded by EEG in relation to behavioral performance of 7 to 10 year old typically developing children performing a visuospatial covert attention task. To this

end, we designed a new, engaging, child-friendly task, relying on validated principles of visuospatial covert attention task. Results of this study were described in **Chapter 6**.

This study was able to show that 7 – 10 year old children already display a pattern in lateralized alpha modulation that is similar to adults. While alpha power (8 – 12 Hz) decreased contralateral to the attended visual hemifield, it increased contralateral to the unattended visual hemifield. However, in adults, lateralized alpha modulation predicted a cueing benefit (faster response on valid trials compared to invalid trials) (ter Huurne et al., 2013). In children we found the opposite pattern; lateralized alpha modulation negatively predicted the response time on *invalid* trials. Children with a large cueing effect also showed less alpha modulation (in particular in the left hemisphere) and displayed a significantly stronger bias to the right visual hemifield than children with a small cueing effect. Left hemisphere alpha modulation was correlated with the magnitude of the bias to the right visual hemifield. Note that a rightward bias is thought to change as a function of age, being more common in children and elderly than in young adults (Takio et al., 2013, and see *Development of attention* in **Chapter 1**).

The association between an increased ability to modulate alpha activity and a smaller benefit of the cue was inconsistent with what was previously found in adults. A possible explanation of these results is that the functional role of alpha oscillations changes with age. However – as more elaborately discussed in **Chapter 6** – it may also be that the development of attention disengagement, thought to be part of the stimulus-driven ventral stream, develops later than alertness and orienting, thought to be part of the top-down dorsal stream. I interpret results from a very recent study (Murphy, Foxe, & Molholm, 2015) to be in line with this hypothesis. This study investigated alpha oscillations of 8 – 34 year old individuals while performing a cross-modal selective attention task. They found that alpha oscillations – like in adults – were already stronger for auditory cued trials compared to visually cued trials in 8 – 12 year old children. More importantly, they found that 8 – 12 years old children had more difficulty to switch modality from one trial to the next and were far more disturbed by the addition of a distractor from the uncued modality than adolescents and young adults (Murphy et al., 2015). Another recent study investigated developmental changes in functional connectivity of attention networks in typically developing children (7 – 12 years old) and adults (18 – 31 years old) (Farrant & Uddin, 2015). When studying the dorsal attention network, they found

that children showed greater functional connectivity with regions within the network, while adults showed greater functional connectivity with regions outside the network. When studying the ventral attention network, they showed that the network was more functionally connected to the salience network in children than in adults (Farrant & Uddin, 2015). How exactly this asymmetric development of attention processes can explain the results that we found is not clear yet. At least in adults, the ventral attention network has been shown to causally influence the dorsal attention network (Sridharan et al., 2007) and both networks are thought to be necessary for reorientation of attention (Corbetta, Patel, & Shulman, 2008). Therefore the degree of functional connectivity between the salience network and the ventral attention network may influence the dorsal attention network, hence alpha oscillations. How this phenomenon could explain higher alpha modulation with smaller response times on invalid trials in children remains to be investigated in future research.

Furthermore, our data suggest that children may have an enhanced ability to attend to the right visual field since an increased ability to modulate alpha activity was associated with a smaller bias to the right visual hemifield. This rightward bias seems to be explained by alpha oscillations in the left hemisphere not being strong enough to break the attentional focus. A bias to the right visual field is generally observed in children (see *Development of attention* in **Chapter 1**). However, an attenuation of the typical leftward bias, i.e. a rightward shift in spatial bias, is also seen with time spent on the task, reduced arousal, and increased perceptual load in healthy adults (Bellgrove et al., 2004; Benwell et al., 2013; Dodds et al., 2008; Dufour, Touzalin, & Candas, 2007; Fimm, Willmes, & Spijkers, 2006; Manly et al., 2005; Matthias et al., 2010; Newman, O'Connell, & Bellgrove, 2013; Perez, Garcia, & Valdes-Sosa, 2008; Perez et al., 2009). More specifically, changes in the alpha band activity have been measured with attentional load (Perez et al., 2009) and time spent on task (Newman et al., 2013) as well. The asymmetric development of attention processes in children (Farrant & Uddin, 2015) may therefore not only be responsible for a negative relationship between alpha modulation and the cueing benefit, but also for the rightward bias.

All in all, we were able to demonstrate that 7 – 10 year old children already displayed a similar pattern of lateralized alpha modulations during covert attentional performance as adults displayed in previous research. However, children showed an opposite relationship with behavioral performance.

4. *How do lateralized alpha modulations observed in children with ADHD relate to typically developing children and previous observations in adults with and without ADHD?*

Although twenty-two typically developing children and twenty-two children with ADHD from the second study sample were available for analyses, we focused on the analysis of 9 typically developing boys and 17 boys with ADHD in **Chapter 7** (the sample of typically developing children is largely overlapping with the sample of **Chapter 6**). Since we did not counterbalance gender during recruitment, significantly more boys ended up in the ADHD group than in the typically developing group. More importantly, the ADHD group contained only 5 girls. Due to the previously found influence of gender within ADHD on for instance attentional performance (Hasson & Fine, 2012), the functional neuroanatomy of working memory (Valera et al., 2010), and resting state EEG (Dupuy et al., 2013a; Dupuy, Clarke, & Barry, 2013b), in combination with the large influence of gender on the current results (see *The influence of gender* in **Chapter 7**) and the notion that genuine etiological differences seem to underlie gender differences within ADHD (Arnett et al., 2015), we decided to continue analyses with boys only.

In **Chapter 6** we showed that typically developing children show a similar pattern of lateralized alpha modulation as healthy adults do. In **Chapter 7**, we explored whether boys with ADHD differ from typically developing boys with respect to lateralized alpha modulation. Previous research in adults led us to believe that children with ADHD would not be able to maintain lateralized alpha modulation until target onset (ter Huurne et al., 2013). A cross-modal attention task in children with ADHD showed that significant alpha modulation was absent in these children (Mazaheri et al., 2010) and that alpha activity was relatively diminished compared to controls during encoding of a working memory task (Lenartowicz et al., 2014). What lateralized alpha modulation in boys with ADHD would look like during covert attentional performance was – to our knowledge – not investigated yet.

Results of this study showed that alpha activity in typically developing boys, like the results in **Chapter 6**, was similar to previous results of healthy adults; it decreased in the hemisphere contralateral to the attended hemifield, whereas it relatively increased in the other hemisphere. However, in boys with ADHD this hemispheric lateralization in the alpha band was attenuated compared to typically developing boys. A robust relation with behavioral performance was lacking in both groups.

Why boys with ADHD differ from typically developing boys with respect to lateralized alpha modulation can be explained within a top-down control framework. That is, alpha oscillations are thought to be part of the dorsal frontoparietal network and under top-down control (see *Discussion* of **Chapter 7**; Capotosto et al., 2009; Marshall et al., 2015). Therefore, results of the current study suggest a deviant activation of this network in boys with ADHD. In line with this idea, a meta-analysis of 55 fMRI studies showed hypoactivation in ADHD relative to controls in the frontoparietal network and ventral attentional network (Cortese et al., 2012). Furthermore, deviant connectivity within this network has been related to symptoms of impulsivity, opposition-defiance, impaired response inhibition, and attentional control in children with ADHD (Cortese et al., 2012). If top-down control influence within the frontoparietal network is affected in ADHD, this may explain the difference found in alpha modulation in the occipital cortex. To explore this possibility, measurement of anatomical pathways, using Diffusion Tensor Imaging, could supplement electrophysiological data. That is, tract volume of anatomical pathways connecting prefrontal control areas to posterior regions, have been shown to vary with alpha modulation in healthy adults; individuals displaying greater alpha and gamma modulation in one hemisphere had relatively greater tract volume in that hemisphere (Marshall, Bergmann, & Jensen, 2015). If deviant anatomical pathways would be measured in the same individuals as those with deviant alpha oscillations, this would suggest a frontal origin of deviations within the dorsal frontoparietal network.

In addition to the investigation of top-down control influence on alpha modulation, influence of the dopaminergic pathway could provide insight in the underlying mechanism of ADHD. Drug treatment, among which most common is the prescription of methylphenidate, is the first choice of treatment in children with severe ADHD (see *Training neuronal oscillations* in **Chapter 1** for guidelines from the National Institute for Health and Care Excellences), resulting in successful management of ADHD symptoms in about 56% of the patients (Swanson et al., 2001). Methylphenidate is a catecholamine reuptake inhibitor with dopamine agonistic effects in the basal ganglia, and both dopamine and noradrenalin agonistic effects in cortical brain areas (Arnsten, 2006). Differences between medication-naive children with ADHD and controls have been shown to normalize with methylphenidate by up-regulating fronto-striato-thalamo-cerebellar and parieto-temporal attention networks and down-regulating orbitofrontal activation for reward processing (Rubia, 2009). Dopaminergic neurons are known to influence activity in frontal structures and seem to play a role in various

cognitive processes, amongst others the allocation of attention (Nieloullon, 2002) and gating information (van Schouwenburg, Aarts, & Cools, 2010). Future research should therefore investigate the interplay between dysfunctional neurotransmitters in ADHD and the ability to modulate alpha oscillations during covert attention. A way to investigate this would be to test children with ADHD both on- and off-medication in medication-naive children.

Furthermore, the study described in **Chapter 7**, focused on boys only. When both genders were studied (see *Results for both genders* in the appendix of **Chapter 7**), no difference between ADHD and typically developing children was found with respect to alpha modulation. The majority of previous studies have shown that girls have a maturational lag in the EEG compared to boys (Clarke, 2001a). Interestingly, Mazaheri et al. (2010), who found that 8 – 12 year old children with ADHD did not show significant alpha modulation on a cross-modal attention task, mainly studied boys (TD boys: N = 13, girls: N = 11; ADHD boys: N = 10, girls: N = 2). In a later study with similar findings, 35% of the individuals were female (Mazaheri et al., 2014). However, these were 12 – 17 year old adolescents and therefore developmental gender differences may already have equalized in this age-range. Furthermore, girls have been shown to have a significantly lower alpha frequency than boys until 16 years of age (Chiang et al., 2011). In **Chapter 2,** in which we did not differentiate gender, we showed that a subgroup of children with ADHD displayed a low individual alpha peak frequency. The fact that girls on average have a *lower* alpha frequency than boys (not to be confused with a *low* individual alpha peak frequency compared to age-averages (Arns et al., 2008) and therefore are more alike children with ADHD in this respect, could explain why no difference in alpha modulation was found when both genders were studied. All in all, gender differences in electrophysiological development may account for different findings when taking into account girls in addition to boys. However, these are speculations since only 5 girls with ADHD were included which does not allow for drawing any valid conclusions.

In summary, we showed that boys with ADHD did not display a similar pattern of lateralized alpha modulation during covert attentional performance as typically developing boys, or as adults in previous research. Boys from neither group showed a relationship between lateralized alpha modulation and behavioral performance. For girls, we could not confirm these findings due to a low sample-size.

Keyfindings and conclusions

Resting-state measurements of neuronal oscillations in children with ADHD (**Chapter 2**) showed that:

- as expected, the theta/beta power ratio and theta power were positively related to the ADHD core symptoms. This relationship strengthened when controlling for individual alpha peak frequency, although correlations did not significantly differ from one another.
- 21% of the children showed a (supposed) overlap between their individually determined alpha band and the conventional theta band.
- neurocognitive performance did not show any relationship with the theta/beta power ratio or theta.

The double-blind randomized placebo-controlled study investigating EEG-neurofeedback:

- found results in line with a large meta-analysis (Sonuga-Barke et al., 2013) that concluded that EEG-neurofeedback does not have proven efficacy as a treatment for children with ADHD (**Chapter 3**).
- did not demonstrate superior effects of EEG-neurofeedback on neurocognitive functioning (**Chapter 4**).

A systematic review of the existing literature on the neurocognitive outcome of EEG-neurofeedback:

- was unable to find a firm indication of superior neurocognitive improvement after EEG-neurofeedback compared to control conditions (**Chapter 4**).

Therefore, studies in this dissertation:

- do not support significant benefits of EEG-neurofeedback in its current "care as usual" form on symptomatic and neurocognitive functioning of children with ADHD (**Chapter 3** and **Chapter 4**).
- do not provide conclusive evidence for the presence or absence of the efficacy of EEG-neurofeedback in the treatment of ADHD. To provide this, there is a need to set-up a well-designed study that ensures optimal implementation and embedding of the training, and possibly incorporates different forms of neurofeedback (**Chapter 5**).

Typically developing children performing a covert attention task (**Chapter 6**):

- showed alpha lateralization patterns that did not predict an attentional cueing benefit.
- had stronger left alpha modulation if they were less influenced by spatial cueing.
- displayed a bias to the right hemifield if they were more influenced by spatial cueing.

Boys performing a covert attention task (**Chapter 7**):

- showed adult-like hemispheric alpha lateralization if typically developing.
- lacked hemispheric alpha lateralization during attention allocation if diagnosed with ADHD.
- had significant stronger alpha lateralization if typically developing than if diagnosed with ADHD.

Clinical implications & direction for future research

This dissertation included studies with a theoretical perspective and studies with a clinical application character. Still, future follow-up studies of the studies with theoretical focus may *lead* to clinical application because the findings provide us with useful clues on the underlying mechanism of ADHD.

The findings with respect to EEG-neurofeedback have direct clinical implications; guidance for children with ADHD and their parents with respect to current EEG-neurofeedback treatment should be in line with the actual findings described in this dissertation. These findings do not provide conclusive evidence for the presence or absence of the efficacy of EEG-neurofeedback in the treatment of ADHD. Therefore, the (partial) reimbursement of health insurance companies can be questioned at this stage.

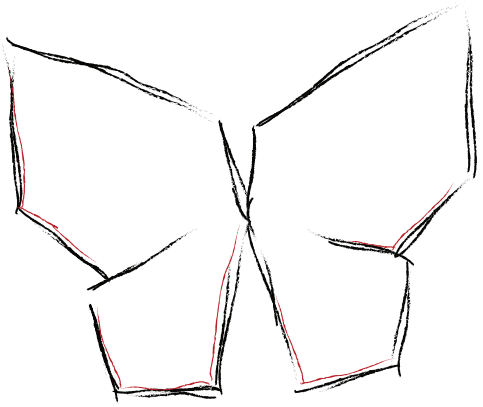
Other possible clinical implications of this dissertation are less straight forward, but therefore not less valuable. For instance, the second chapter of this dissertation studied a low individual alpha peak frequency displayed in a subgroup of children with ADHD. A low individual alpha peak frequency has previously been shown to be important because of its relation with non-response to stimulant medication in ADHD (Arns et al., 2008). This is an example of how theoretical studies may provide information possibly relevant for clinical practice. Further unraveling electrophysiological characteristics of ADHD could be used to predict individual treatment outcome.

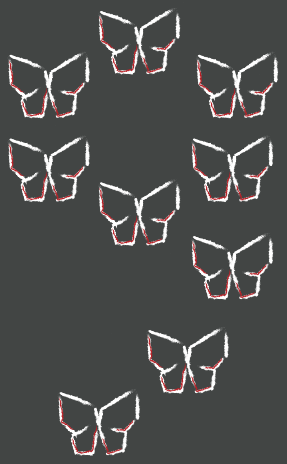
While useful clues on the underlying mechanism of ADHD were established in this dissertation, there is ample work to be done by future research. First of all, inconsistencies of electrophysiological resting-state studies should be overcome by using similar methodology as much as possible, for instance by setting up one large multi-site study with coherent methodology. Furthermore, creating a bridge between the great bulk of literature on electrophysiological data during resting-state and during task performance could provide valuable new insights. In particular, whether similar deviations exist during resting-state and task performance and whether they have the same origin is still unclear.

The need to investigate EEG-neurofeedback with a solid study-design is discussed in great detail in **Chapter 5**. In addition to the need for improved study protocols, EEG-neurofeedback itself may undergo optimization. EEG-neurofeedback is currently based on deviances during resting-state. However, it would be interesting to find out how deviant oscillatory activity during suboptimal task performance can be manipulated to improve task performance. If robust measures of cognitive performance, known to deviate in ADHD, would be used to establish an a-priori hypothesis of a new form of EEG-neurofeedback, this would create a new, promising approach compared to the current empirically driven treatment studies. Based on the findings in this dissertation, I cautiously propose to develop and investigate an EEG-neurofeedback treatment in which lateralized alpha modulation is aimed to be enhanced during performance on a covert attention task. The main question for such a new treatment should still be whether the treatment (also) leads to improvement of other domains than the trained domain, ultimately leading to improvement in daily functioning.

To understand the underlying mechanisms of ADHD it is crucial to understand healthy development as well. Therefore, future research should investigate the development of the attentional networks further, in particular the development of the dorsal and ventral attentional network, with a special focus on the visual bias to the right visual hemifield that we found in our results and an additional exploration of the influence of top-down control development. Next, future studies should shed light on whether alpha modulations are deviant in ADHD due to deviant top-down control within the frontoparietal network and whether a dopamine and noradrenalin agonists, such as methylphenidate affect these deviations. The influence of gender should also be further unraveled to further understand the underlying mechanisms and to be able to adapt treatments to specific needs.

In conclusion, the studies described in this doctoral dissertation answered four research questions (see *Answers to the research questions* in this chapter). However, the results also yielded new research questions and provide directions for future research. Results of such future studies will provide further insight in the underlying mechanisms of ADHD and ultimately lead to potential new treatments for children with ADHD.





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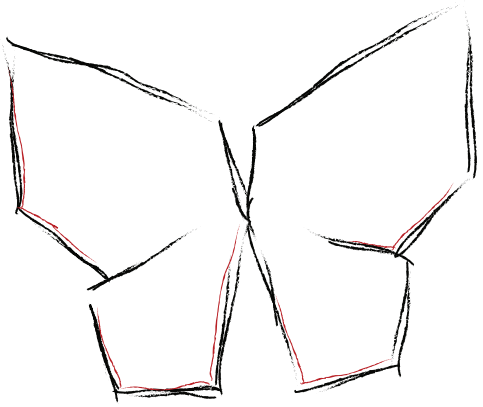


APPENDICES

Nederlandse samenvatting

Achtergrond

Dit proefschrift is een weergave van mijn zoektocht naar de ontwikkeling van potentieel nieuwe behandelingen voor kinderen met aandachtstekort/hyperactiviteitsstoornis (ADHD). ADHD wordt gekenmerkt door een langdurig patroon van aandachtsproblemen en/of hyperactiviteit en impulsiviteit dat doorgaans begint in de kinderleeftijd en een negatieve invloed heeft op het dagelijks functioneren (American Pychiatric Association, 2013). Het is momenteel een populair onderzoeksonderwerp en dat heeft een reden; een ADHD diagnose draagt een last met zich mee voor zowel de betrokken gezinnen als de gehele maatschappij. In de onderzoeken beschreven in dit proefschrift hebben we nadruk gelegd op zowel wetenschappelijke kwaliteit als klinische relevantie.

ADHD komt tegenwoordig voor bij 5 – 7% van de schoolgaande kinderen en drie keer zoveel bij jongens als bij meisjes (Willcutt, 2012). De eerste omschrijvingen van ADHD symptomen zijn al zeker drie eeuwen oud. Zo is er bijvoorbeeld een beschrijving uit 1775 gevonden (Barkley & Peters, 2012). De terminologie van de symptomen is door de jaren heen veel veranderd en er is nog veel onduidelijk over de onderliggende oorzaak van deze stoornis.

Er wordt gedacht dat meerdere genetische en omgevings- risicofactoren elk individuele effecten hebben die gezamenlijk de ontvankelijkheid voor ADHD beïnvloeden (Faraone et al., 2015). Deze complexe oorzakelijkheid komt overeen met de grote variëteit in expressie van de ADHD diagnose. Grote variëteit wordt gezien in neurcognitieve beperkingen in verschillende domeinen (later toegelicht), de hoge mate van psychiatrische comorbiditeit (het hebben van meerdere psychiatrische stoornissen tegelijk), en een breed scala aan afwijkingen in structuur en functioneren van de hersenen (Faraone et al., 2015).

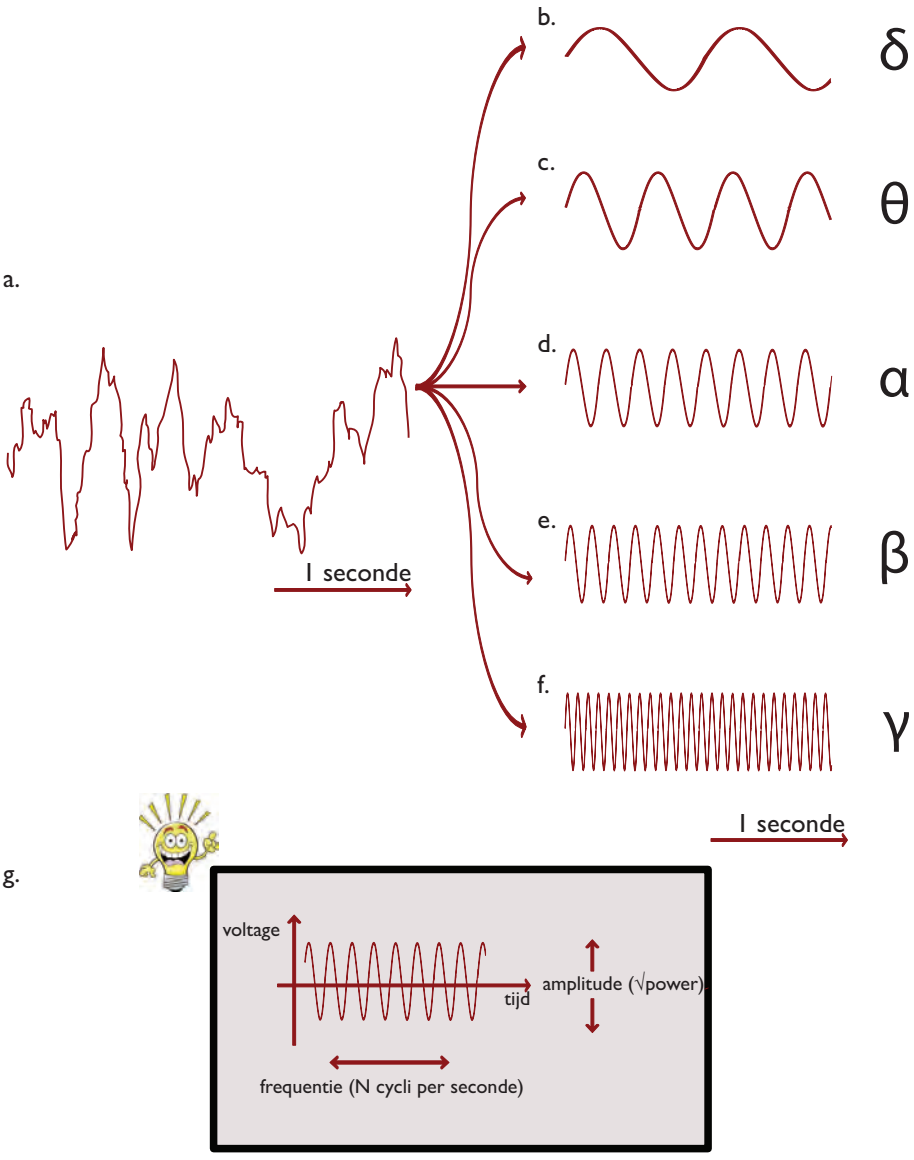
Neurocognitieve afwijkingen zijn afwijkingen in mentale vaardigheden die geassocieerd worden met bepaalde hersenactiviteit. Dergelijke afwijkingen zijn – in relatie tot ADHD – beschreven in de aandacht, de uitvoerende functies, belonings-gerelateerde processen, en tijdsinschatting (Tsal et al., 2005; Martinussen et al., 2005; Willcutt et al., 2005; Sonuga-Barke et al., 2008, 2010; de Zeeuw et al., 2012; Noreika, Falter, & Rubia,

2013). Zoals reeds benoemd zijn er grote verschillen in neurocognitieve afwijkingen tussen patiënten met ADHD (Faraone et al., 2015).

Dit proefschrift richtte zich met name op de *'elektrofysiologische afwijkingen'* die bij ADHD gezien worden. Voordat per hoofdstuk wordt beschreven wat in dit proefschrift onderzocht is, licht ik toe wat met deze afwijkingen bedoeld wordt.

Elektrofysiologie is een methode om hersenactiviteit in kaart te brengen middels het meten van elektrische activiteit op de schedel. Deze methode werd aan het begin van de 19e eeuw al geïntroduceerd (Berger, 1929) en wordt doorgaans afgekort met *'EEG'* (elektro encefalogram). Een EEG-signaal bestaat uit een optelsom van elektrische hersengolven, ofwel *'neuronale oscillaties'*, die los van elkaar kunnen worden onderzocht nadat er een zogenaamde *'Fourier Transformatie'* is uitgevoerd. De hersengolven worden dan ingedeeld in frequentie-groepen, afhankelijk van de snelheid waarmee het signaal beweegt. De hoogte van de golf bepaalt hoe sterk of zwak de signaal-activiteit aanwezig is en wordt aangeduid met de term amplitude of power. Deze kenmerken van het EEG-signaal staan uitgelegd in *Figuur 1*, evenals de indeling van de verschillende frequentie-groepen. Verschillende frequentie-groepen worden geassocieerd met verschillende (neurocognitieve) functies. Sommige kenmerken van het EEG-signaal veranderen gedurende de ontwikkeling.

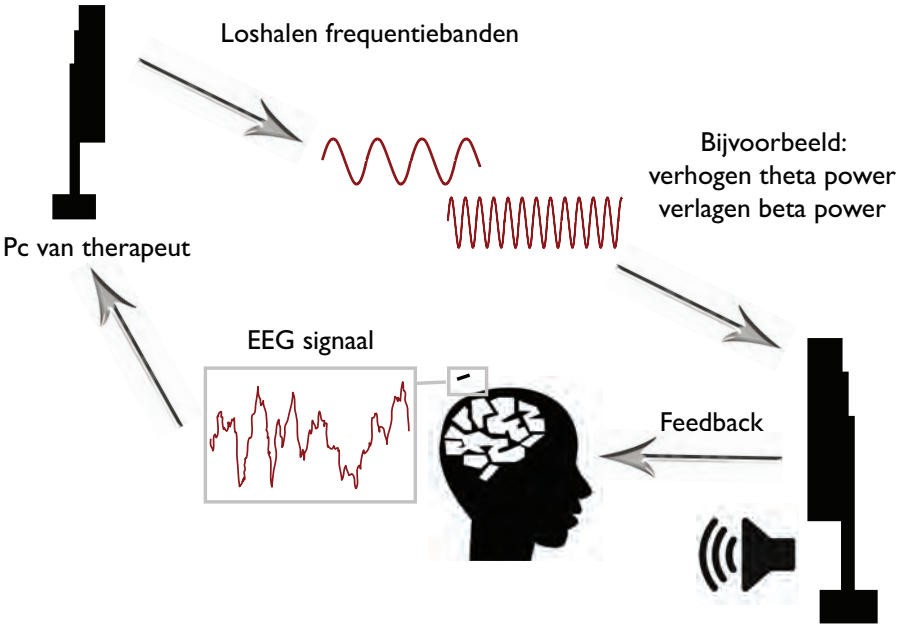
Wanneer EEG gemeten wordt terwijl kinderen met ADHD zo rustig en stil mogelijk zitten, wordt over het algemeen meer activiteit in de theta-band gevonden dan bij kinderen van dezelfde leeftijd zonder ADHD (Arns, Conners, & Kraemer, 2013). Daarnaast wordt bij kinderen met ADHD vaak minder activiteit in de beta-band gevonden, deze bevinding is echter minder consistent doordat een kleine groep van deze kinderen juist meer activiteit in de beta-band laat zien (Arns et al., 2013). Deze twee frequentiebanden worden regelmatig als één maat in een ratio weergegeven; beta-activiteit gedeeld door theta-activiteit. Redenen om deze zogenaamde theta/beta power ratio met voorzichtigheid te gebruiken, zijn in dit proefschrift besproken (**Hoofdstuk 2**).



Figuur 1. *(a).* Een EEG-signaal bestaande uit een optelsom van elektrische hersengolven die in banden kunnen worden ingedeeld. Activiteit van verschillende frequentiebanden wordt uit het EEG-signaal gehaald door middel van een '*Fourier Transformatie*'. Elke frequentieband heeft een andere snelheid waarmee het signaal trilt/oscilleert. Dit wordt weergegeven in Herz (Hz). *(b-f).* De verschillende frequentie-groepen, aangeduid met de bijpassende Griekse letter *(b).* Delta oscillaties (< 4 Hz). *(c)* Theta oscillaties (4 – 8 Hz). *(d)* Alfa oscillaties (8 – 12 Hz). *(e)* Beta oscillaties (12 - 30 Hz). *(f)* Gamma oscillaties (> 30 Hz). *(g)* Illustratie van verschillende kenmerken van hersengolven.

Met betrekking tot de alfa frequentieband is gevonden dat de snelheid van deze golven in een subgroep kinderen met ADHD, lager ligt dan bij kinderen zonder ADHD. Bij volwassenen met ADHD is een verschil geconstateerd in de hoeveelheid alfa-activiteit tijdens het doen van een aandachtstaak. In dit proefschrift werd zowel de invloed van de snelheid van alfa golven onderzocht (**Hoofdstuk 2**) als de activiteit tijdens het uitvoeren van een aandachtstaak (**Hoofdstuk 6** en **7**).

Aangezien medicatie om verschillende redenen niet *altijd* de voorkeursbehandeling is, is er vraag naar alternatieve behandelmethoden. EEG-signalen zouden de basis kunnen vormen voor een innovatieve behandeling. EEG-neurofeedback, zoals onderzocht in dit proefschrift, beoogt afwijkende hersengolven te meten en vervolgens te trainen om op die manier het (hersen-)functioneren te verbeteren. In *Figuur 2* is te zien hoe EEG-neurofeedback in zijn werk gaat. De mate waarin activiteit in een bepaalde frequentieband gemeten wordt, ofwel de hoogte van golven die vooraf op een bepaalde snelheid zijn geselecteerd, wordt op een computerscherm gevisualiseerd (dit kan op verschillende manieren gebeuren). Vervolgens wordt de persoon/het kind, door middel van visuele en auditieve feedback, beloond wanneer de activiteit richting de gewenste activiteit verandert. Op deze manier wordt beoogd te leren hoe de hersenactiviteit beïnvloed kan worden. Er bestaat een wereldwijde discussie over de effectiviteit van EEG-neurofeedback bij kinderen met ADHD (en kinderen en volwassenen met andere stoornissen). Er is geen onomstotelijk bewijs gevonden voor de effectiviteit van deze behandeling, aangezien er een duidelijk verschil is gevonden tussen resultaatmetingen gedaan door personen die wel wisten wat voor behandeling het kind had gehad (meestal de ouders) en resultaatmetingen gedaan door personen die dit niet wisten (meestal de leerkracht). In dit proefschrift werd EEG-neurofeedback onderzocht op een placebo-gecontroleerde manier, dat wil zeggen dat zowel kinderen en hun ouders als de onderzoekers niet wisten welke behandeling ze kregen (**Hoofdstuk 3** en **4**). Ook werd de toekomst van EEG-neurofeedback kritisch bediscussieerd (**Hoofdstuk 5**).



Figuur 2. Schematische weergave van een EEG-neurofeedback opzet.

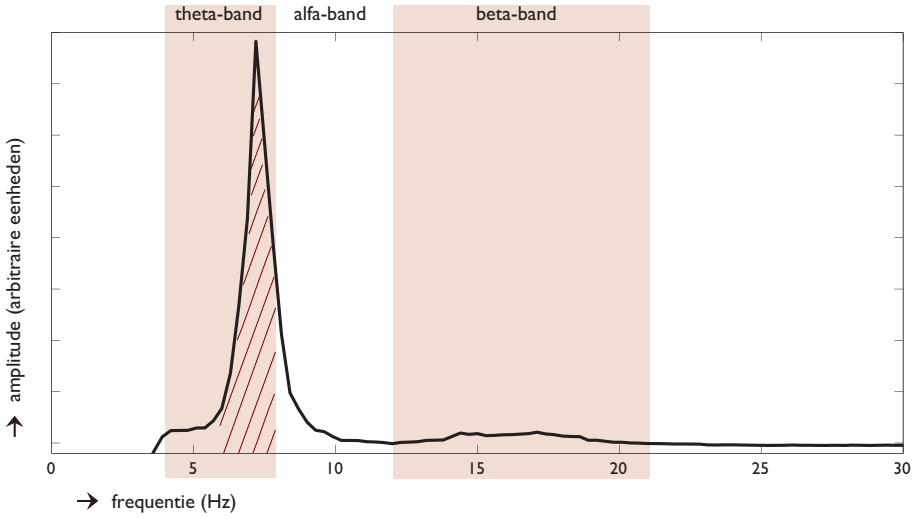
De resultaten per hoofdstuk

Dit proefschrift bestaat uit 6 empirische hoofdstukken, **Hoofdstuk 2 t/m 7**. De resultaten van deze hoofdstukken zullen kort worden samengevat.

In **Hoofdstuk 2** werd gekeken naar de invloed van een langzaam tempo van de hersengolven in de alfa frequentieband, aangeduid met een lage *individuele alfa piek frequentie* (*IAPF*). We onderzochten in hoeverre langzame individuele alfa-golven (een lage IAPF) de relatie tussen de theta/beta power ratio en de relatieve theta power in rust, ten opzichte van neurocognitief en gedragsmatig functioneren beïnvloedde. We hebben dit bestudeerd omdat uit eerder onderzoek bleek dat een lagere IAPF verantwoordelijk was voor de verhoogde theta/beta power ratio in een subgroep bij kinderen met ADHD. Dit leidde tot de suggestie dat verhoogde theta power (als onderdeel van de verhoogde theta/beta power ratio) als meest robuuste bevinding bij ADHD - als het gaat over hersengolven in rust - soms verkeerd wordt geïnterpreteerd. Dit zou dan veroorzaakt worden door een lage IAPF, waardoor deze

mee wordt genomen in de schatting van theta power (zie *Figuur 3*). Om de invloed van de IAPF te onderzoeken op de correlaties tussen de theta/beta power ratio en de relatieve theta power enerzijds en neurocognitief en gedragsmatig functioneren anderzijds, werden data over hersengolven in rust, neurocognitief functioneren en ADHD-kernsymptomen geanalyseerd. Data werden verkregen van de voormeting van de studie 'PANther'. Voor 38 kinderen (8 – 15 jaar) waren data van hersengolven in rust en ADHD-kernsymptomen scores beschikbaar. Voor 32 kinderen waren ook neurocognitieve data voorhanden. De IAPF werd gemeten door het gebruik van zowel de ogen-open als de ogen-dicht conditie; alfa golven worden doorgaans vele malen meer gemeten in de ogen-dicht conditie en daarom helpt bepaling van het verschil tussen de condities om de snelheid van alfagolven nauwkeurig individueel te bepalen. De power werd geanalyseerd op basis van de ogen open conditie. Een significant positieve relatie werd gevonden tussen de theta/beta power ratio en de totale score op de ADHD-kernsymptomen en voor theta/beta als theta power in relatie tot de score op de subschaal hyperactiviteit. Deze relaties werden sterker wanneer rekening werd gehouden met de individuele variatie in de IAPF. Acht van de 38 kinderen (21%) lieten een verlaagde IAPF zien (een IAPF van 9 Hz of lager), waardoor een overlap ontstond tussen hun IAPF en de standaard theta-band. Een relatie tussen de theta/beta power ratio en/of relatieve theta power in rust en het neurocognitief functioneren werd niet gevonden. De resultaten van dit onderzoek bevestigden dat de theta/beta power ratio en relatieve theta power inderdaad correleren met de ADHD-kernsymptomen. De bevindingen suggereren verder een belangrijke rol voor de IAPF in de onderliggende elektrofysiologie bij ADHD, omdat de IAPF de bovengenoemde correlatie beïnvloedde.

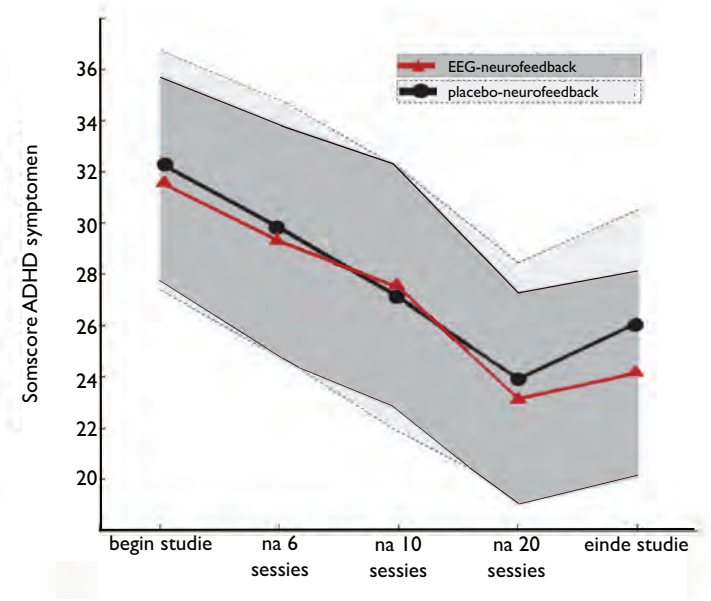
Vervolgens werd in **Hoofdstuk 3** een studie bij kinderen met ADHD beschreven naar de effectiviteit van EEG-neurofeedback op de ADHD-kernsymptomen en het globaal klinisch functioneren en de veiligheid van deze behandeling zoals deze gegeven wordt in de dagelijkse klinische praktijk. In **Hoofdstuk 4** werd dezelfde studie beschreven waarbij ditmaal de effectiviteit van EEG-neurofeedback op neurocognitief functioneren bij kinderen met ADHD onderzocht werd. **Hoofdstuk 4** bevatte tevens een systematische 'review' over dit onderwerp. Daarnaast werd het EEG gedurende de sessies geanalyseerd met als doel te onderzoeken of er toename van het leren hersenactiviteit te beïnvloeden plaatsvond gedurende de EEG-neurofeedback. Dit onderzoek betrof een dubbelblinde, semi-gerandomiseerde, placebo-gecontroleerde studie. Kenmerken van een dergelijke studie worden hierna



Figuur 3. Dit figuur laat een dataset zien van hoe activiteit van de alfa frequentieband kan leiden tot een foute interpretatie van de schatting van theta-power. De lijn geeft de hoeveelheid activiteit (amplitude) per hersengolf-snelheid (frequentie) aan. De getinte vlakken geven de verschillende frequentiebanden weer. De gestreepte zone onder de alfa-curve (specifieke bepaling van de individuele alfa-band staat uitgelegd in hoofdstuk 2) geeft het gebied aan waarin alfa power onterecht de theta power schatting zal verhogen.

beschreven. Eenenveertig kinderen (8 – 15 jaar) met ADHD werden semiwillekeurig toegewezen aan EEG-neurofeedback of placebo-neurofeedback voor 30 sessies met een frequentie van tweemaal per week. Gecontroleerde indeling (stratificatie) werd toegepast voor leeftijd, elektrofysiologische kenmerken en medicatiegebruik (vandaar '*semi*' willekeurig). Alle betrokkenen in deze studie, behalve de EEG-neurofeedbacktherapeut, waren "blind" ten aanzien van groepstoewijzing. Een breed palet aan vragenlijsten en neurocognitieve taken werd voor en na de behandeling afgenomen. Deze neurocognitieve taken waren uitgekozen op grond van de veronderstelde neurocognitieve disfuncties bij kinderen met ADHD (aandacht, executief functioneren, belonings-gerelateerde processen en tijdsinschatting). Hoewel beide groepen verbetering van ADHD-kernsymptomen lieten zien, kon dit onderzoek niet aantonen dat EEG-neurofeedback superieur is ten opzichte van de placebo neurofeedback (zie *Figuur 4*). Het zelfde gold voor het globaal klinisch functioneren. Er werden geen relevante bijwerkingen gevonden. Haalbaarheid van deze studie-opzet ten aanzien van de geïmplementeerde placebo-neurofeedback, waarbij het feedback signaal gebaseerd was op een gesimuleerd EEG signaal, bleek uit de bevinding dat het raden van de groepstoewijzing niet beter was dan op basis van kans. Zowel op

groepsniveau als op individueel niveau werden geen significante effecten gevonden op neurocognitief functioneren ten gunste van EEG-neurofeedback. In lijn met de bevindingen van deze studie, liet ook de systematische review over dit onderwerp geen superieur effect zien van EEG-neurofeedback op neurocognitief functioneren. Daarnaast werd geen bewijs gevonden voor toegenomen neurale regulatie na EEG-neurofeedback. Er werd bovendien geen onderbouwing gevonden voor de hypothese dat een normalisatie van het EEG zou leiden tot een verbetering van symptomen aangezien de kinderen die een verbetering van symptomen lieten zien, geen eenduidige normalisatie van het EEG lieten zien. De studies naar de effectiviteit van EEG-neurofeedback bij kinderen met ADHD toonden geen superieur effect aan van de behandelconditie ten opzichte van de placebo conditie. Het is mogelijk dat methodologische aspecten en tekortkomingen van deze studies oorzaak zijn van het niet vinden van grote specifieke behandeleffecten zoals die gevonden worden bij ADHD-medicatie; hoewel de resultaten niet inconsistent waren, maar niet statistisch aanwezig waren op alle niveaus.



Figuur 4. Gemiddelde van de totale somscores op de vragenlijst die ADHD symptomen mat per meetmoment en het 95% betrouwbaarheidsinterval.

Hoofdstuk 5 beoogde een overzicht te bieden van hoe toekomstig onderzoek naar EEG-neurofeedback eruit zou moeten zien om zicht te krijgen op de mogelijke effectiviteit van EEG-neurofeedback. De vraag werd gesteld of de afwezigheid van sterk bewijs het gevolg zou kunnen zijn van methodologische beperkingen. Er werd een discussie over dit onderwerp geschreven zonder het gebruik van nieuwe data en gesteld dat de daadwerkelijke effectiviteit van EEG-neurofeedback moet worden getest met een sterk onderzoeksdesign, optimale implementatie en inbedding van de behandeling. Daarnaast kunnen andere meer innovatieve vormen van neurofeedback uitgeprobeerd worden. We concludeerden dat hoewel tot dusverre de werkzaamheid van EEG-neurofeedback bij kinderen met ADHD niet overtuigend is aangetoond, toekomstig onderzoek zal moeten uitwijzen of er misschien toch potentie in de behandeling zit.

De laatste twee empirische hoofdstukken richtten zich op hersenactiviteit in de alfa frequentieband tijdens het uitvoeren van een aandachtstaak.

Bewijs wordt steeds sterker dat alfa oscillaties een functionele onderdrukkende rol zouden hebben, vooral afkomstig van studies die ruimtelijke aandacht onderzoeken bij gezonde volwassenen. Dat wil zeggen dat hersenactiviteit in de alfa frequentieband juist in die hersengebieden gemeten wordt waar géén activiteit verwacht zou worden op basis van de (aandachts-)taak. Of modulatie van alfa oscillaties een vergelijkbare functionele rol spelen in normaal ontwikkelende kinderen was aan het begin van dit onderzoek nog onduidelijk. Daarnaast bleek uit eerder onderzoek bij volwassenen met ADHD dat dergelijke alfa modulatie afwijkend was ten opzichte van volwassenen zonder ADHD. Bij kinderen met ADHD waren alfa-golven nog niet tijdens een aandachtstaak onderzocht. Het doel van de studie omschreven in **Hoofdstuk 6** was om alfa modulatie in kinderen te karakteriseren in relatie tot hun aandachtsprestatie. Het doel van de studie omschreven in **Hoofdstuk 7** was vervolgens om alfa modulatie in dezelfde context te vergelijken tussen kinderen met en zonder ADHD. Met dit doel werd alfa activiteit (8 – 12 Hz) aan de achterkant van het hoofd in kinderen (met en zonder ADHD) tussen de 7 en 10 jaar oud met EEG gemeten, terwijl ze een 'visuospatiële coverte aandachtstaak' uitvoerde (een taak waarin de aandacht naar een bepaald punt verschoven wordt met behulp van een ruimtelijk aanwijzing, zonder de ogen te bewegen).

Bij kinderen zonder ADHD, omschreven in **Hoofdstuk 6**, vonden we dat alfa activiteit verminderde in de hersenhelft schuin tegenover het aandachtsveld en vermeerderde in de andere hersenhelft. Merk hierbij op dat visuele informatie voornamelijk in de hersenhelft schuin tegenover het visueel veld verwerkt wordt. De resultaten zijn dus tegenovergesteld en wijzen op onderdrukking van activiteit in plaats van verhoging van activiteit. Ook vonden we dat de mate van gelateralizeerde alfa modulatie (verschil in alfa activiteit tussen hersenhelften als reactie op het uitvoeren van de taak) de prestatie op de aandachtstaak voorspelde door het doen van een negatieve voorspelling op de reactietijd van '*invalide cues*' (testpogingen waar de aandacht niet op gericht was). Opvallend is dat kinderen die minder beïnvloed werden door de ruimtelijke aanwijzing (de '*cue*'), ook de kinderen waren met een duidelijk gelateralizeerd alfa modulatie patroon. Er werd significant sterkere alfa lateralisatie gezien in de linker hersenhelft dan in kinderen die meer beïnvloed werden door de ruimtelijke aanwijzing. Daarnaast was de voorkeur voor het rechter visuele veld, zoals deze over het algemeen gezien wordt in kinderen, significant kleiner of afwezig bij de kinderen die het minst door de ruimtelijke aanwijzing beïnvloedt werden. Voor alle kinderen samen gold dat de mate van voorkeur voor het rechter visuele veld positief gerelateerd was aan het vermogen om alfa activiteit te moduleren. Concluderend hebben we in **Hoofdstuk 6** laten zien dat het patroon van alfa oscillatie modulatie tijdens aandacht al in 7 – 10 jaar oude normaal ontwikkelende kinderen aanwezig is. Hoewel een vergelijkbaar patroon in volwassenen wordt gezien, zijn de consequenties voor gedrag verschillend.

Bij kinderen met ADHD, omschreven in **Hoofdstuk 7**, vonden we andere resultaten. Hoewel 30 kinderen met ADHD en 30 kinderen zonder ADHD (overlappend met de resultaten van kinderen die werden getest in **Hoofdstuk 6**) werden getest, richtte de analyse in **Hoofdstuk 7** zich op 17 jongens met ADHD en 9 jongens zonder ADHD. Resultaten van data-analyse van de meisjes wees in een andere richting. Omdat we hier geen conclusies over konden trekken gezien de kleine groepsgrootte (we hadden slechts 5 analyseerbare datasets van meisjes met ADHD), is gekozen voor een weergave van alleen de resultaten van de jongens. Alfa activiteit in jongens zonder ADHD was vergelijkbaar met eerdere resultaten in volwassenen en resultaten in **Hoofdstuk 6**; alfa activiteit ging naar beneden in de hersenhelft aan dezelfde kant als waar de aandacht gericht was terwijl deze omhoog ging in de tegenovergestelde hersenhelft. Jongens met ADHD lieten echter geen duidelijke alfa lateralisatie zien. Verder was er in beide groepen geen robuuste relatie met

de prestatie op de taak. Concluderend was de vaardigheid om alfa activiteit te moduleren tijdens het richten van de aandacht duidelijk aanwezig in jongens zonder ADHD, maar niet duidelijk in jongens met ADHD. Deze resultaten geven aanleiding om de rol van alfa modulatie als onderliggende mechanisme bij ADHD verder te onderzoeken.

In **Hoofdstuk 8** werden alle resultaten op een rij gezet en bediscussieerd.

Conclusies

Uit de resultaten van dit proefschrift kunnen verschillende conclusies worden getrokken.

De resultaten van **Hoofdstuk 2** laten een relatie zien tussen de conventionele theta/beta power ratio en theta power enerzijds en gedragsmatig functioneren anderzijds. Daarnaast suggereren de resultaten dat de frequentie waarop alfa piekt de eerder onderzochte relaties tussen elektrofysiologie en gedragsmatige uitkomsten zou kunnen beïnvloeden.

Het onderzoek beschreven in **Hoofdstuk 3** en **Hoofdstuk 4**, levert geen bewijs voor een positiever effect van de huidige klinisch toegepaste EEG-neurofeedback op symptomen en neurocognitief functioneren in kinderen met ADHD, dan een placebo behandeling. Desalniettemin, zoals besproken in **Hoofdstuk 5**, is er ruimte voor verbetering in de behandeling en de behandelprotocollen voordat definitief kan worden geconcludeerd dat neurofeedback geen effect heeft.

In **Hoofdstuk 6** hebben we laten zien dat 7 – 10 jaar oude kinderen al een gelateraliseerd alfa modulatie patroon laten zien tijdens de uitvoer van een visuospatiele coverte aandachtstaak, net als volwassenen in voorgaand onderzoek. Kinderen lieten echter een tegenovergestelde relatie met prestatie op de taak zien.

Ten slotte toonden de resultaten beschreven in **Hoofdstuk 7** dat jongens met ADHD geen vergelijkbaar patroon van gelateraliseerde alfa modulatie lieten zien tijdens de uitvoer van een visuospatiele coverte aandachtstaak als jongens zonder ADHD of volwassenen uit voorgaand onderzoek. Zowel jongens met als zonder ADHD lieten geen relatie zien tussen de alfa hersengolven en prestatie op de

aandachtstaak. Voor meisjes konden we geen van deze bevindingen betrouwbaar bevestigen vanwege een kleine groepsgrootte.

Klinische implicaties

Dit proefschrift behelsde studies met een theoretisch perspectief en studies met een klinisch toepasbaar karakter. Vervolgstudies van de studies met theoretische focus kunnen desalniettemin leiden tot klinische toepasbaarheid omdat de bevindingen kunnen leiden tot meer inzicht in de onderliggende mechanismen van ADHD.

De resultaten van de onderzoeken naar EEG-neurofeedback hebben directe klinische implicaties. Voorlichting aan ouders en hun kinderen met ADHD over EEG-neurofeedback dient in lijn te zijn met de actuele onderzoeksresultaten. Het belangrijkste advies voor toekomstig wetenschappelijk onderzoek is het optimaliseren van (de methodologie van) eerdere studies om de mogelijk specifieke en unieke effecten van EEG-neurofeedback verder te onderzoeken. Op basis hiervan kan een meer definitieve uitspraak gedaan worden over de effectiviteit van deze behandelmethode bij kinderen met ADHD.

Andere mogelijke klinische implicaties van dit proefschrift zijn minder eenduidig, maar daarmee niet minder waardevol. In **Hoofdstuk 2** werd bijvoorbeeld de invloed van een lage individuele alfa piek frequentie in een subgroep van kinderen met ADHD onderzocht. Een dergelijk lage alfa piek frequentie werd in eerder onderzoek gerelateerd aan non-respons op stimulerende medicatie (Arns et al., 2008). Dit is een voorbeeld van hoe theoretische studies informatie kunnen leveren die mogelijk relevant is voor de klinische praktijk. Het ontrafelen van elektrofysiologische kenmerken van ADHD zou kunnen leiden tot zogenaamde 'biomarkers' die individuele behandeluitkomsten kunnen voorspellen.

About the author

Madelon Vollebregt was born on September the 21th 1987 in The Hague, the Netherlands. In 1993 she moved with her family to Rhenen. After completing highschool (VWO) at Pantarijn Wageningen in 2005, she studied Neuropsychology and Cognitive Neuroscience at the Radboud University Nijmegen, where she also lived during college days.

She gained a Master degree both in the fields of Neuropsychology and Cognitive Neuroscience (in 2010 and 2012 respectively). In addition, she followed the majority of the courses of Clinical and Developmental Psychology. As clinical part of the Master in Neuropsychology, she worked at the memory polyclinic of hospital Gelderse Vallei Ede, supervised by Monique de Lugt. As research part of the master, she started working at RadboudUMC and Karakter Child- and Adolescent Psychiatry, both in Nijmegen. At first, Madelon performed the neuropsychological assessments for both the PANther project (Project Adhd & eeg-Neurofeedback therapy), in which the efficacy of EEG-neurofeedback in 8 – 15 year old children with ADHD was being investigated, and the WORM project (WORking Memory training), in which the efficacy of Cogmed working memory training in 5.5 – 7.5 year old children with ADHD was being investigated. She was supervised by Jan Buitelaar and Dorine Slaats, with daily supervision of Marieke Lansbergen. Her activities soon expanded with EEG measurements, performed at the Donders Institute, Centre for Cognitive Neuroimaging.

When Madelon decided to expand her education with the Cognitive Neuroscience Research Master, she set-up her own project called SHARK (Study on the inter-Hemispheric Alpha Ratio in Kids with adhd), in which alpha-oscillations were compared between 7 – 10 year old children with and without ADHD. To this end, she jointed the research group of Ole Jensen, daily supervised by Niels ter Huurne and Johanna Zumer.

After gaining her second Master degree, she continued to work on the three aforementioned projects. Two of which (PanTHER and SHARK) became part of this

doctoral dissertation. She started to work intensively with Martine van Dongen-Boomsma, who set-up PanTHER and WORM, analyzing and documenting the results of these two projects. Next, Madelon finished the SHARK project, mostly by herself. In addition, she soon expects a University Teaching Qualification (UTQ) by having documented the experience she gained in guiding study groups, giving lectures, supervising Master students, and developing teaching materials. She also organized masterclasses that were given on high schools to enthuse young students for brain research.

Proud to have finished her PhD-trajectory within the predefined period, Madelon immediately went on to work as senior researcher at Research Institute Brainclinics in January 2016. There, among other things, she supervises researchers and continues the research line that was started within her doctoral dissertation. She will remain affiliated to the Donders Institute as well. Her main focus will be on the investigation of 'personalized medicine' in ADHD.

Being married to Martijn van Beek, Madelon is called Madelon van Beek-Vollebregt for the non-academic world. Together they have a daughter called Elise (2015).

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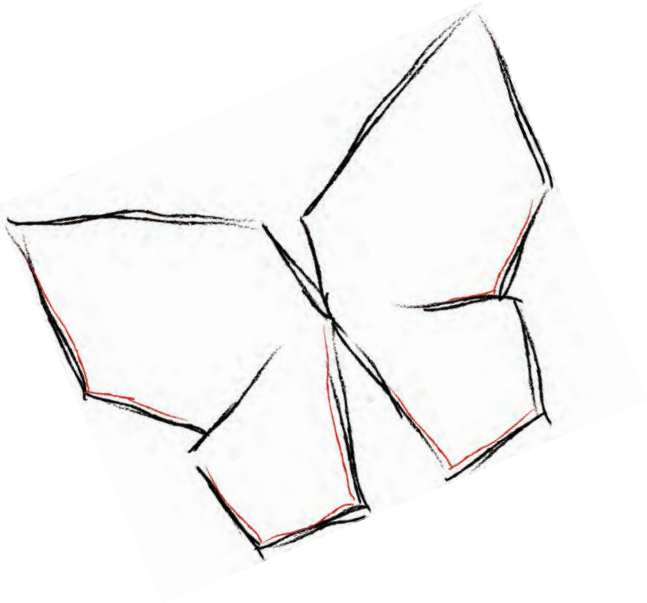

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